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THE DERMATOLOGIST AND THE PSYCHIATRIST

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AND
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FOR THE past few decades dermatologists and psychiatrists alike have become increasingly aware that emotions and cutaneous changes are often related. There is an abundant literature today which concerns itself with observations (and attempted interpretations) of this relationship. This recognition is in line with the modern concept of disease, which predicates that all functions and processes of the human organism are interrelated and that disturbance in one sphere has its effect on other, apparently unrelated, spheres.

One finds, however, that, although there is general agreement by dermatologists and psychiatrists that their fields overlap, there is no agreement as to the nature of the essential relationship. The area of controversy centers in part around the question of etiology. It is agreed that some emotional disturbance often accompanies and follows some cutaneous disorders, but it is a question whether or not certain types of cutaneous lesions owe their origin to disturbances in the emotional sphere. Many dermatologists and psychiatrists are of the belief that this causal relation does indeed exist and have cited as proof reports of cures of cutaneous lesions after psychiatric treatment of patients who have had cutaneous conditions complicating their mental symptoms. However, many are equally firm in their conviction that emotional factors have no etiologic significance in dermatology.

The probabilities are that differences of opinion on this point stem from differences in the basic concept of disease. The tendency in medicine to describe succeeding events in terms of causality, although constantly discredited by logicians and those concerned with the philosophy of science, received a strong practical impetus from the discoveries of bacteriology. These discoveries led, in the early days, to an unqualified and unjustified renewal of the belief that disease was

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

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"caused," and caused in particular by the invasion of demoniac representatives with Latin names. Actually the manifestations of disease are the product of many interacting forces, internal and external, physical and chemical, social and psychologic. This last-mentioned concept has come to be generally accepted in theory; in practice, however, the pragmatic dermatologist who is called on to treat a dermatitis resulting from contact with poison ivy, for example, is not inclined to go further than the simple, even though fallacious, assumption that the poison ivy caused the dermatitis. The assumption, even though false, has its practical value. In many other dermatoses, however, it is not only philosophically unsound but also of no practical usefulness to assume that any such direct "causation" can be designated. Thus, whether an emotional state "causes" a dermatitis is not debatable, or answerable, in spite of the fact that opinions about it, pro and con, are held and constantly advanced. It would be better to say that conditions of disturbed personality equilibrium may (or may not) combine with other factors to produce in some persons a condition for which they seek help from a dermatologist but for which they might (perhaps) equally well seek help from a psychiatrist.

Overconcern with this fallacious question of causal relation has obvious detrimental implications with respect to therapy. In the light of present limited knowledge of the fundamental mechanisms of this relation, it seems sufficient at this time to acknowledge that an interrelation does exist; that it is true not only that the presence of a cutaneous lesion has an important bearing on a patient's mental outlook but also that changes in the emotional state of the patient are reflected in the cutaneous disorder, whatever the pathologic basis for the cutaneous eruption may be.

Most modern dermatologists recognize this essential relation but often feel handicapped by their uncertainty of how to recognize, evaluate and treat the emotional factor adequately. When a patient presents himself to the dermatologic clinic for treatment, the physician is faced with this dilemma: Shall he treat only the skin and thus play into the neurotic needs of the patient by avoiding the psychologic problems, or shall he attempt to deal with the manifest or underlying emotional factors and find himself out of his sphere of proficiency, and perhaps beyond his depth? How can he determine or evaluate the psychologic components? If he decides to deal with the emotional factors, what shall he do about them? Or shall he send the patient to a psychiatrist? These are the problems which dermatologists constantly face.

There is no easy solution to these problems; evaluation of the degree of a patient's emotional difficulties and best management of them are not simple matters. The evolutionary development of the personality, its tentative adjustments and the developments of emotional conflicts

and maladjustments are notoriously complex. In an attempt to simplify the problem, various evaluations of patients in terms of so-called personality types have been devised. Such descriptive labels are valuable, however, only so far as they serve as beacons in an intricate labyrinth of mental functioning. For a similar reason, formulations of the clinical syndrome in terms of simple conceptions and the use of these formulations as a basis for therapy are likely to be both erroneous and misleading and hence lead to disappointment with therapeutic results.

The patients who come to the dermatologic clinic or to the dermatologist's office presenting a cutaneous condition may be, for practical purposes, entirely free from any psychopathologic disorder or maladjustment. As we have already indicated, however, they frequently give the dermatologist reason for thinking that there is some degree of maladjustment, and the first questions may be these: Assuming that the emotional condition is not entirely unrelated to the cutaneous one, how severe is this emotional maladjustment? How accessible is it to medical approach? To what extent does the patient recognize or accept the relationship of the cutaneous disturbance to the other evidences of his maladjustment to life?

The answers to these questions determine the most effective procedure for the dermatologist to follow in treatment.

There are four or five possibilities. There are, for example, many cases in which the dermatologist himself should use a combination of psychotherapy and local treatment. For example, a 40 year old unmarried bank clerk had an acute attack of anxiety because of discovery of a herpetic lesion, which he believed to be chancre, on his genitals. Perhaps this case will seem too simple; it is used merely as a paradigm. Every dermatologist can supply many examples of successfully combined local and psychologic treatment.

Then there are patients whose cutaneous lesions should be treated exclusively on a symptomatic basis, even though much psychopathologic disturbance may be evident. For example, a 25 year old hospital aide while on duty suddenly attacked his companions. He was hospitalized and subsequently was observed to respond to auditory hallucinations and to exhibit other symptoms which led to a diagnosis of paranoid schizophrenia. From this he was convalescing when he suddenly manifested an outbreak of generalized urticaria.

A third group of patients with cutaneous disease is perhaps best treated by psychiatrists unassisted. For example, a 35 year old married lawyer had been periodically incapacitated by alcohol for ten years before he sought treatment by a dermatologist for an exudative eruption on his arms and legs. He stated that these lesions would appear

each time he visited his mother, who constantly criticized him for his method of handling finances. The relation of these criticisms to his alcoholism eluded him.

Finally, there are patients who should be treated concurrently by the dermatologist and the psychiatrist. For example, a 23 year old ex-sailor sought treatment for psoriasis which involved his entire body, neck and extremities. He was extremely self conscious about his lesions and had avoided friends because he felt they would resent his presence. Although greatly interested in sports he did not participate in them because of fear of exhibiting his body.

We should probably add a fifth group, the members of which are perhaps best treated if left alone by both dermatologists and psychiatrists!

Of these five possibilities, that of combined medical and psychologic therapy by the dermatologist is probably the most frequently indicated. Our reasons for believing this statement are as follows:

First, the patient himself has selected his therapeutist when he seeks the dermatologist for treatment. He comes with the assurance that he is being treated by a specialist who has a large body of special knowledge pertaining to every aspect of the patient's manifest cutaneous disease. He may or may not be aware of emotional problems or recognize their importance, for his orientation is in connection with the cutaneous lesion, which, directly visible to the naked eye, stands as mute but eloquent testimony to his illness. Such a patient expects local treatment, and such treatment satisfies his concept of the physician as one who understands the nature of his illness and does something concrete about it. Production of this feeling in itself contains elements of psychologic therapy, and without such local treatment the patient may be uninterested in or disturbed by an initial approach to other factors in his illness.

In the second place, if the object of treatment is not to reorganize the patient's personality but, rather, to restore him to the degree of adjustment or relative adjustment that he had been able to make before the onset of his cutaneous symptoms, psychotherapy by the dermatologist will not need to be highly technical or greatly prolonged and will (and does) often yield excellent results.

Other reasons which favor the use of psychotherapy by the dermatologist might be added. But it is more important to stress the fact that the dermatologist who would thus supplement his therapeutic program should do so scientifically. Haphazard psychotherapy is little different from acquiring an armful of assorted salves or lotions and applying them indiscriminately to all cutaneous lesions. It is true, of course, that acceptable and even excellent results may sometimes be obtained with the use of such bland supportive psychotherapeutic tech-

nics as reassurances and the recommendation of rest. But this is true only in the same sense that the application of bland ointments to all cutaneous changes would result in some cures. The fact remains that utilization of psychotherapeutic technics requires of dermatologists, or anyone else who uses them, an understanding of the general principles of psychopathology and psychotherapy on which they are based.

In the course of these studies, dermatologists will no doubt become particularly interested in factors in cutaneous diseases which immediately attract the attention of psychiatrists, such as the factor of exhibitionism, the phenomenon of compulsive scratching, the problem of self-directed destructive impulses and the phenomenon of narcissistic preoccupation with surfaces of the body. In the pursuit of such interests it is hoped that the dermatologists will avoid the error sometimes made by psychiatrists, of seeing these trends and phases too large and the total meaning of the pathologic changes in the skin in the patient's life too small.

SUMMARY

The awareness that there is an essential relation between emotions and cutaneous conditions would seem to be a first consideration for adequate therapy. Once this is recognized, various possibilities of treatment present themselves. These possibilities include (1) symptomatic treatment of the cutaneous lesion alone, regardless of possible emotional maladjustment, (2) combined treatment of the medical and psychologic components by the dermatologist, (3) concurrent treatment of the patient by both dermatologist and psychiatrist and (4) treatment by the psychiatrist alone.

Of these four possibilities of treatment, the combined medical and psychologic therapy by the dermatologist is probably the one most frequently indicated. But competence in the proper handling of the emotional factors by the dermatologist can come only from an understanding of fundamental psychiatric principles.

Menninger Sanitarium.

ABSTRACT OF DISCUSSION

Dr. John H. Lamb, Oklahoma City: I agree that there is a small group of patients whom the dermatologist can help by psychotherapy. Attempts have been made, particularly by English dermatologists, such as Klauber, Rogerson and Watts, to link definite personality traits to certain dermatologic diagnoses.

I am not sure that any certain types of psychic traits or obsessional neuroses were linked to any particular cutaneous manifestations in the present short series of selected cases, in which definite emotional factors were evident. There are, of course, the exceptions of pruritis vulvae et ani, which is in many cases definitely linked to the psychosexual sphere, and of the nervous eczemas of childhood, in which the child-parent adjustment and early or late adjustments in family relations play a definite role, as Rogerson suggested.

Lewis and Cormia, in their excellent report, have outlined well the office management for psychosomatic studies of the dermatoses. I believe that the crux of successful treatment of small stresses is in the physician-patient relationship. The physician must give the patient the feeling that he is sincerely interested in his welfare and will help him in whatever way he can.

In selected cases, in which one feels that the emotional elements play a large part, the dermatologist should (1) take adequate time to listen to the patient's troubles, (2) confine his therapy to simple and superficial methods, (3) build up the patient's self respect and self confidence, (4) relieve environmental hazards in the patient's life by recommending changes (but give no advice on marriage or divorce) and (5) point out more mature approaches to life's problems, whenever possible.

Dr. S. William Becker, Chicago: Drs. Gottesman and Menninger reaffirm the belief of Bond, who, in discussing a paper by Stokes before this Section, stated that a patient has a better chance of obtaining relief through the first physician consulted than if he is referred to many physicians, including a psychiatrist.

We all have seen the beneficial results of reassurance and rest, the latter of which seems to be badly needed by our urban patients. Lack of a sense of fatigue in most patients with functional dermatoses furnishes us with a practical method of classifying the eruption as representative of perversion of this valuable sensation. Demonstration of the relation of acetylcholine to some urticarias, by Hopkins, and of reproduction and aggravation of dyshidrosis by injection of methacholine chloride U. S. P. (mecholyl chloride®), by Leon Goldman, are strongly suggestive of a nervous mechanism. It is also known that simple measures often fail in the treatment of factitial eruptions, so that psychiatric care is necessary in their management.

Having employed home-made psychotherapy for years, with good results, and having been warned of its dangers, I was glad to be reassured by Dr. Roy Grinker, in his paper entitled "Every Doctor a Psychiatrist," that such management is not particularly disastrous. Of course, the measures are combined with local and systemic treatment for the presenting dermatosis. When a dermatologist recognizes the neurogenic factors in functional disorders of the skin, acceptable results can usually be obtained. One of the most important elements that has already been recognized is the need for one spending time with the patient. When I see a patient for the first time, especially someone from out of town, I spend no less than one hour with him. I think this amount of time is absolutely necessary. Dr. Wagner, of the University of Michigan, emphasized that the most important element in getting acquainted with these patients is to sit down and listen to them.

If dermatologists can be trained in the general principles of psychopathology and psychotherapy, as suggested by the authors, even better results may be expected.

Dr. Karl A. Menninger, Topeka, Kan.: Dr. Gottesman and I appreciate your courtesy in inviting us to talk to the Section on Dermatology about something which we think is of unusual interest. My impression would be that dermatologists know more about psychiatry than psychiatrists know about dermatology. In addition to the technical advantage which dermatologists have in working with their own patients, there is a certain atmosphere that is important to the psychiatrist. It is important, I think, because there is such a determined effort on the part of the thoughtful dermatologist and psychiatrist working together.

In the old days, the attitude was, "Well, we have no relationship. Your patients are that kind; our patients are this kind." Now the attitude is, "Please don't refer those patients to us, because we think you can do better than we can, in

most instances." I suppose this relation will go on through other stages, as there is a constant effort to find out, for practical purposes, which specialist is best fitted to treat certain kinds of patients. As a result, the psychiatrist begins to learn what the dermatologist is like. He begins to discover that the dermatologist is not what he thought, someone sitting in a corner, surrounded with salves and slapping a different kind on each patient.

Some psychiatrists have reported a great deal of success in the treatment of conditions that dermatologists have become quite discouraged with, such as psoriasis.

I should like to emphasize what Dr. Lamb and Dr. Becker said. Perhaps what we as psychiatrists have contributed is really not psychiatric at all, but a sort of return to the original principle of medicine, namely, that the physician, whether dermatologist or proctologist or surgeon or psychiatrist, should be a physician first and a specialist second, that being a physician means that everything about the patient which is making him uncomfortable, unhappy or unproductive is of importance to the physician and that not only the physician but also the patient must recognize it as important.

Therefore, it seems accurate to say that the most important thing that psychiatry can do is to emphasize this attitude, this concept of the human being as a totality. In the first paper on the program, which was extremely interesting to me, the emotional factors which exacerbate the sensation of itching and the pleasure derived from scratching were not stressed. What curious personality factors are present that exaggerate and distort the pleasant sensation of scratching? Nearly everybody likes to have the back, or some other part of the body, scratched. The curious psychologic factor is that in some persons the sensation seems to be concentrated at the orifices. This is not merely a physical or mechanical fact; it is also a psychologic fact. It involves the whole question of pleasure and pain and the question of selection of the parts of the body. Obviously, it involves the psychologic setup. Hence, one should not describe a person as though the only part of his personality of interest to one were the perineum. One must be interested in that person's total adjustment to life. I do not mean to imply that the discussion did not touch on this factor, rather, its enormous importance constantly impresses us psychiatrists. It is vital how happy or how miserable a person is, and why. Whether one calls his misery an expression of anxiety, or a localized expression of anxiety, is less important than the realization that people have many ways of expressing their internal pain and that these ways of expressing it may involve structures, as well as merely functions, of the body.

The illusion that only functions of the body are affected by one's internal feelings has long since vanished. The structure of the body is also affected, and dermatologists know this, because they, more than any other group, have seen the results of such conditions as chronic edema and chronic congestion.

The knack of dealing with these dermatoses is quite distinct from the attitude of dealing with only what is important. It has seemed to me, in teaching, that one can have a psychiatric attitude without having any psychiatric technics or psychiatric knowledge. One can realize this in one's basic medical knowledge. In addition, some persons have an extraordinary knack of dealing with these dermatoses in a very correct and practical way. In addition to the knack, in addition to the attitude, specialized technics can be developed for use in certain cases.

HISTORY OF DERMATOLOGY, 1847 TO 1947

OLIVER S. ORMSBY, M.D.
CHICAGO

THE HISTORY of dermatology is divided into epochs: ancient, medieval, Renaissance and later, and nineteenth century. The story of dermatology is unfolded by the record of the achievements of its eminent men and by the discovery and development of drugs, chemicals, vaccines, facilities for physical therapy (roentgen rays, radium and a variety of electrical procedures), vitamins, several antibiotic substances (penicillin, streptomycin, BAL [2,3-dimercaptopropanol]) and chemotherapeutic preparations (the arsphenamine group and the several members of the sulfonamide group). These additions to the dermatologic armamentarium have completely revolutionized the practice of dermatology. Were the late Dr. James Nevins Hyde, with whom I was associated for nine years, and who died thirty-seven years ago, to appear in one's office today, he would find everything changed except for roentgen therapy, and even this has been immensely improved through better machines, tubes and facilities for measuring an accurate dosage. Improved laboratory methods have done away with some of the the skill in accurate observation that had developed to a high degree in men who were at their zenith when I began the practice of dermatology, forty-six years ago. At that time, our chief reliance in arriving at conclusions was on clinical observation, with some histopathologic help. Now, the microscopic examination for fungi of various types; examinations of the blood, including the Wassermann and precipitation tests, the examinations in diagnosis of the lymphoblastoma group and various chemical tests for sugar, calcium and other substances; determination of the basal metabolic rate, and other laboratory procedures have served to make the keen clinical observations seem less important; but from my viewpoint they are as important now as at any time and should be impressed on the younger generation of dermatologists.

Only a few of the outstanding dermatologists from various countries during the period of time covered in this paper can be discussed.[1]

Read before the Section on Dermatology and Syphilology at the Ninety-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1947.

1. Pusey, W. A.: The History of Dermatology, Springfield, Ill., Charles C Thomas, Publisher, 1933. (This valuable work has been freely consulted in the preparation of this paper.)

CONTINENTAL EUROPE

Ferdinand Hebra (1816-1880).—Hebra[2] was one of the world's outstanding figures in the field of dermatology, as a clinician, a teacher and a voluminous writer. Students from all over the world attended his clinic in Vienna. He made important investigations on ringworm, and first described rhinoscleroma, in 1872; impetigo herpetiformis, in 1872, and lichen acuminatus, lichen scrofulosus (tuberculosis lichenoides) and Hebra's prurigo. He also did important work in the erythema multiforme group, tinea cruris (eczema marginatum), the xanthomas, pemphigus, urticaria, pruritus and eczema. Among his great contributions are his "Atlas der Hautkrankenheiten," published between 1856 and 1876, and his "Lehrbuch der Hautkrankenheiten," completed by his successor, Kaposi. He received honors from foreign medical and scientific societies the world over, and in Vienna he held the title of *Hofrath,* was president of the Vienna Akademie der Wissenschaften and was also president of the Kaiserlichen Gesellschaft der Aertzte of Vienna, the highest honor Austria could confer.

Moritz Kaposi (1837-1902).—Kaposi,[2] son-in-law of and successor to Hebra, successfully carried on the latter's great traditions. Among other diseases described by Kaposi were xeroderma pigmentosum, multiple idiopathic hemorrhagic sarcoma (idiopathic multiple pigmented sarcoma), herpes zoster gangrenous hystericus and folliculitis keloidalis (dermatitis papillaris capillitii), and he was co-author with Hebra in the presentation of rhinoscleroma. His "Atlas of Skin Diseases" (three volumes, 1898, 1899 and 1900) was extensive and most valuable. His treatise "Pathology and Treatment of Diseases of the Skin," translated into French and English, was an outstanding work.

Heinrich Auspitz (1835-1886).—Auspitz[2] was a brilliant pupil of Hebra's. In his "System of Skin Diseases" (1881), in which he made an important classification of diseases of the skin, and his monograph, "General Pathology and Therapy of Skin Diseases," published in von Ziemssen's "Handbuch" (1885), he added important findings in dermatology. The terms parakeratosis and acanthoma were introduced into pathology by him. He also called attention to the bleeding points in psoriasis (Auspitz' sign).

Isadore Neumann (1832-1906).—Neumann[2] established the chair of dermatology and syphilology in Vienna. His treatise on cutaneous diseases went through five editions. He stressed histopathology and made contributions on leprosy. His greatest accomplishment was a treatise on syphilis.

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2. Ravogli, A.: The History of Dermatology, M. Life **33**:492, 1926: Hebra, pp. 522-531; Kaposi, pp. 531-532; Auspitz, pp. 532-535; Neumann, pp. 537-538; Hardy, pp. 507-508.

Filip Joseph Pick (1834-1910).—Pick, another pupil of Hebra's, made Prague an important center of dermatology. He was the first full professor of dermatology in Austria, and with Auspitz he founded the *Archiv für Dermatologie* (1869), of which he was editor for several years.

Other Austrian Dermatologists.—Malassezia furfur was discovered by Eichstedt as the cause of pityriasis versicolor in 1846, and Actinomyces minutissimus, by Felix von Barensprung as the cause of erythrasma in 1862. Only passing notice can be given to A. von Veiel (1806-1879), who founded the institute for cutaneous diseases in Canstatt, and his sons, Ernst (1837-1883) and Theodore (1848—).

E. L. Schwimmer (1837-1883), a student of Hebra's, stimulated the subject of dermatology in Budapest. He was author of the first Hungarian textbook on dermatology, published in 1872. He also made contributions on leukoplakia buccalis in 1878 and on neuropathic dermatoses in 1883.

Heinrich Köbner.—Breslau came into dermatologic prominence through the work of Heinrich Köbner, Oscar Simon and Albert Neisser. Köbner founded the dermatologic clinic in 1861. In 1872, he moved to Berlin, where he became the first president of the Berlin Dermatological Society. He described epidermolysis bullosa and did research work on plant parasites of the skin, mycosis fungoides, leprosy, psoriasis, pemphigus and syphilis.

Oscar Simon (1845-1882).—Simon succeeded Köbner and became head of the Breslau clinic in 1887. He made contributions on localization of cutaneous diseases (1873). He also investigated molluscum contagiosum (1876), cachetic gangrene of the skin (1878), animal vaccines (1879), macula cerulea (1881) and balanoposthitis (1881).

Albert Neisser.—Simon was succeeded in 1882 by Albert Neisser (1854-1916), who was the third to head the Breslau school. His work in histology, pathology, bacteriology, protozoology and immunology was outstanding. He discovered the gonococcus, Neisseria gonorrhoeae, in 1879. Together with Hansen, he stained the lepra bacillus, Mycobacterium leprae, in 1879. He investigated a large number of cutaneous diseases and made important contributions on them. His research completed the establishment of tuberculosis luposa (lupus vulgaris) as a tuberculous disease.

Paul Gerson Unna (1850-1929).—Unna was trained under Hebra and Auspitz. He excelled in the study of pathologic degenerations of the cutis and the development of specific staining methods. He was also an important bacteriologist. His monumental "Histopathology of the Skin" covered the whole domain of diseases of the skin, with an enormous amount of entirely original study. He accomplished all his

magnificent work unaided by state or university and had large numbers of students from all parts of the world, including America. In 1882 he established the *Monatshefte für praktische Dermatologie*. Under Dr. J. M. H. MacLeod, I had a year's training in histopathology (1900-1901). Dr. MacLeod had just returned from a three year study at Hamburg, and his instruction followed the methods of Unna.

Carl William Boeck (1808-1875).—In Scandinavia, Boeck, professor of surgery, dermatology and syphilology in Christiania, wrote extensively on leprosy, much of it with D. C. Danielssen (1815-1894). They described Norwegian scabies (radesyge) and other parasitic diseases of the skin. Carl Boeck also wrote extensively on syphilis. Danielssen's and Boeck's work on leprosy (two volumes, with an atlas) was monumental. They also produced a volume, with an atlas, on parasitic diseases of the skin.

Armauer Hansen (1841-1912).—In 1871 Hansen discovered the lepra bacillus, Mycobacterium leprae, and demonstrated it before the Christiania Medical Society in 1874. Neisser later (1879) confirmed the discovery. Much work was done in Scandinavia on tuberculosis.

Caesar Boeck (1845-1917).—In 1896 Caesar Boeck discussed toxituberculides, bringing together into this classification several different conditions, and in 1910 Darier gave them the name of tuberculids. The sarcoid group also was described in part by Boeck.

Niels R. Finsen (1860-1904).—Finsen, in Denmark, placed the treatment of tuberculosis with ultraviolet rays on a scientific basis and devised a lamp that is used successfully throughout the world in the treatment of tuberculosis luposa.

Italian Dermatologists.—Early Italian writers described pellagra and did fine work on histology of the skin and in the study of industrial diseases. Modern Italian contributors include Tommasoli, Mibelli, Campana and others. The bacillus causing chancroid was described by Ducrey (1888); observations on angiokeratoma were made by Mibelli in 1891 and on parakeratosis in 1893. Giovanni described nodular disease of the hair in 1891 and the histology of keratosis pilaris in 1895. Respighi described hyperkeratoses in 1893, and Majocchi, purpura annularis telangiectodes in 1898.

FRENCH DERMATOLOGISTS

French dermatology has been represented by so many brilliant minds that it is difficult to select the few that the limitations of this paper permit. Hôpital Saint-Louis has been the center of dermatologic development both in training of men and in the study of dermatoses. Among many important figures must be named Alibert, Biett, Cazenave, Rayer, Gibert, Devergie, Bazin and Darier.

J. L. B. Alibert (1768-1837).—While the time of Alibert precedes the period with which this paper is concerned, he is mentioned on account of his part in making Hôpital Saint-Louis one for cutaneous diseases. He first described mycosis fungoides and named it, and he also described keloid.

Laurent Théodore Biett (1781-1840).—Biett is mentioned along with Alibert on account of his work as a founder of French dermatology. Cazenave, Gibert, Devergie, Rayer, Hardy and Bazin were almost all students of Alibert and Biett.

P. L. A. Cazenave (1802-1877).—Cazenave, with Schedel, produced a "Manual of Diseases of the Skin" (1828), which recorded Biett's work and teachings. Cazenave first described pemphigus foliaceus (1850); studied lupus erythematosus, named by him lupus erythematodes (1851), and founded the first French journal of dermatology, *Annales des maladies de la peau et de la syphilis* (1843-1852).

Pierre Francois O. Rayer (1793-1867).—Rayer was an outstanding figure in medicine, pathology and dermatology. He studied and analyzed the lesions of the skin, described adenoma sebaceum and proved by animal experimentation that glanders was contagious—a specific disease and not a form of tuberculosis. He also was the author of a textbook on dermatology, which was translated into English. He was a distinguished physician and citizen of France.

Camille Melchoir Gibert (1797-1866).—Gibert was a pupil of Biett and one of the masters of Hôpital Saint-Louis. He described and named pityriasis rosea. He contributed much to the therapy of cutaneous diseases and syphilis and was a member of the Academy of Medicine.

Alphonse Devergie (1798-1879).—Devergie succeeded Biett at Hôpital Saint-Louis. He published a "Treatise on Dermatology" in 1857, was one of the founders of the dermatologic museum at Hôpital Saint-Louis and described and named pityriasis rubra pilaris.

Ernest Bazin (1807-1878).—Bazin[3] studied scabies thoroughly and revolutionized the treatment of the disease at Hôpital Saint-Louis. He used epilation, in addition to parasiticides, in the treatment of ringworm and favus. He first described acne varioliformis (1831), under the title "acne pilaire." He also described folliculitis keloidalis (dermatitis papillaris capillitii), under the title "acne keloid." He also first described hydroa vacciniforme and tuberculosis indurativa (erythema induratum, Bazin's disease). He was well informed on the natural sciences and did much work on syphilis.

3. Beeson, B. B.: Ernest Bazin: Sketch of His Life and Works, Arch. Dermat. & Syph. **20**:866 (Dec.) 1929.

Alfred Hardy (1811-1893).—Hardy [2] was physician to Hôpital Saint-Louis and later to Hôpital de la Charité. He and Bazin interned together at Hôpital Saint-Louis and were close colleagues in dermatology. He first described syphilitic leukoderma (pigmentary syphilid) and made contributions to the subjects of tuberculosis luposa, tuberculous ulcers, scleroderma and eruptions associated with bromide intoxication. He grouped tinea capitis, tinea corporis and tinea barbae as forms of cutaneous trichophytosis. With Bazin's and Hardy's investigations, dermatology was placed on a clearcut basis as to nosology, nomenclature, symptomatology and diagnosis.

David Gruby [4] (1810-1898) described Microsporum audouinii and Trichophyton endothrix between 1842 and 1845. Fifty years later Sabouraud rediscovered these fungi and gave Gruby full credit.

Rudolf Virchow (1821-1902).—Much light was thrown on cutaneous pathology by Virchow. His publications included studies on pathologic pigment, the anatomy of hair follicles, pemphigus vulgaris (1855), normal and pathologic anatomy of the nails (1857), glanders (1857), onychomycosis (1860), lepra (1861), verrucae (1863), molluscum contagiosum (1865), prickle cells (1865), cutaneous tuberculosis (1865) and xanthoma multiplex (1871), as well as the "History of Leprosy" (1860).

Emile Vidal (1825-1893).—Vidal [5] described lichen chronicus simplex, made studies in histopathology of the skin, impetigo, echthyma and pemphigus neonatorum and, with Leloir, wrote on tuberculosis luposa. In 1872 he published studies on dermatitis exfoliativa. He was one of the founders of the Société française de dermatologie et de syphiligraphie and one of the editors of the *Annales*.

Ernest Besnier (1831-1909).—Besnier succeeded Bazin in Hôpital Saint-Louis in 1872. He was an eminent teacher and had as followers such famous dermatologists as Brocq, Sabouraud, Leredde, Balzer and Thiberge. He translated Kaposi's "Dermatology" into French, making many invaluable additions in the translation. With Vidal and Fournier, he founded the Société française de dermatologie et de syphiligraphie, in 1889. With Brocq and Jacquet he edited "La pratique dermatologique" from 1901 to 1904 (four volumes).

Henri Hallopeau (1842-1919).—His first great work was in pathology. His treatise on this subject ran through six editions, in twenty-five years. From 1884 to 1907 he devoted his time to dermatology at Hôpital Saint-Louis. With Leredde, he wrote a textbook on dermatology. He was a voluminous writer, having published several hundred

4. Beeson, B. B.: David Gruby, M. D., 1810-1898, Arch. Dermat. & Syph. **23**:141 (Jan.) 1931.

5. Beeson, B. B.: Emile Vidal, Arch. Dermat. & Syph. **22**:115 (July) 1930.

articles. He first described lichen planus atrophicus (lichen sclerosis) and dermatitis vegetans. He also contributed important articles on idiopathic atrophy, acanthosis nigricans, premycotic mycosis fungoides and trichotillomania.

Henri Leloir (1855-1896).—Leloir was chief of the clinic of Vournier. He wrote much on pathology and first described lupus vulgaris erythematodes.

Louis Brocq (1856-1928).—Brocq was a dermatologist of great ability. He was a voluminous writer, and his contributions were important. He described the plaque type of parapsoriasis and contributed to the literature on bullous and exfoliative dermatoses.

Raymond Jacques Sabouraud (1864-1938).—Sabouraud's [6] lifework consisted in a study of the mycoses. His studies were carried on in the municipal laboratory of the city of Paris, created for the study of the mycoses, of which laboratory he was made chief, and in Hôpital Saint-Louis. He contributed numerous articles on mycoses and in 1910 published his monumental work of over 1,000 pages, "Les teignes," which covered the entire subject, including a comprehensive classification. He did investigative work on the alopecias, eczema, the streptococci and pityriasic dermatoses. He was recognized as an expert diagnostician.

Jean Darier (1856-1938).—He received the degree of Doctor of Medicine in 1885. He was assistant in Ranvier's histologic laboratory at the Collège de France and was also chief of Fournier's laboratory. He was on the staff of Hôpital Broca and Hôpital Saint-Louis and founded the museum of cutaneous pathology at Hôpital Saint-Louis. He was a contributor to both the old and the new "La pratique dermatologique." His textbook on dermatology went through four editions. He made notable contributions on keratosis follicularis (Darier's disease), acanthosis nigricans, pseudoxanthoma elasticum, tuberculids, Darier-Roussy sarcoid and the dyskeratoses. He was popular as a teacher, and his chief pupils were Civatte, Roussy, Flandin and Tzanck.

ENGLISH DERMATOLOGISTS

Sir Erasmus Wilson (1809-1884).—Sir Erasmus was a pupil of Hebra's. He described trichorrexis nodosa (1849), erythema nodosum (1857) and general exfoliative dermatitis (1870) and assembled the various forms of lichen planus into one group in 1869. His "Diseases of the Skin" went through six editions, and he published a dermatologic atlas in 1847. He also published "Lectures on Eczema and Dermatology" (1870-1878). In 1867 he established the *British Journal of Dermatology*, the first publication of its kind in English.

6. Bechet, P. E.: Raymond Jacques Sabouraud, J. Invest. Dermat. **1**:171, 1938.

Tilbury Fox (1836-1879).—He was an able and eminent English dermatologist. He first described dyshidrosis and impetigo. By experimentation he proved impetigo to be contagious. He demonstrated kerion to be a form of ringworm. He described but did not name urticaria pigmentosa, lymphangioma circumscriptum, dermatitis herpetiformis, epidermolysis bullosa and other conditions. He published a treatise, "Diseases of the Skin" (1864), "Lectures on Eczema, Its Nature and Treatment" (1870) and "Endemic Skin Diseases of India" (1876), all standard works on their subjects.

Henry Radcliffe Crocker (1845-1909).—Crocker[7] was one of England's eminent dermatologists. He succeeded Tilbury Fox as head of the department of dermatology at the University College Hospital. His textbook, which went through three editions, represented in large part personal observations of the diseases described. He was a careful observer and a keen diagnostician. In his clinic and at the meetings of the London Dermatological Society and the Dermotological Society of Great Britain and Ireland in 1900 and 1901, and again at the Sixth International Congress of Dermatology in New York, in 1906, I was deeply impressed with his keen ability as a diagnostician. His personal atlas of cutaneous diseases, which work developed from 1893 to 1896, was a masterpiece, with plates drawn from actual cases under his observation. He was one of the founders of the London Dermatological Society (1882). He held membership in dermatologic societies in America, Austria, Italy, France and Germany. Among other diseases he discussed outside his textbook were erythema elevatum diutinum, myoma multiplex, granuloma annulare, xanthoerythroderma perstans, recurring winter and summer eruption and keratosis palmaris et plantaris.

Sir Jonathan Hutchinson (1828-1913).—He was famous as a clinician in both dermatology and syphilology and wrote extensively on leprosy. He first described dermatitis gangrenosa infantum (varicella gangrenosa), in 1882, and also angioma serpiginosum and myxedema of the face. He also described under names of his own several diseases, such as cheiropompholyx, which had previously been described.

Thomas Colcott Fox (1848-1916).—Thomas Fox[7] was a brother of Tilbury Fox and was famed for his ability as a diagnostician. He was physician for diseases of the skin at Westminster Hospital and Medical School for thirty years, beginning in 1883. He was a teacher of note and made many contributions to the literature in the *British Journal of Dermatology*, Allbutt's "System of Medicine" and an annual

7. Little, E. G., in Deliberationes Congressus Dermatologorum Internationalis IX-1, Budapest, September 1935, Leipzig, Johann Ambrosius Barth, 1936: Biographies of Crocker, p. 145; Colcott Fox, p. 146; Galloway, p. 147; Morris, pp. 148-149; Pringle, p. 150.

"Digest of Dermatological Literature" in Wright's "Medical Annals." He was a collaborator with Tilbury Fox in producing the third edition of the "Epitome of Skin Diseases" (1876). Early in his career he was physician to a children's hospital which did special work in tuberculosis and ringworm. He succeeded Radcliffe Crocker as president of the section of dermatology of the Royal Society of Medicine.

Sir James Galloway (1862-1922).—Sir James [7] was appointed physician to the skin department of Charing Cross Hospital in 1894. He was a member of the London Dermatological Society, and later of the section of dermatology of the Royal Society of Medicine, of which he was president in 1917. He was editor of the *British Journal of Dermatology* from 1896 to 1904. A trained pathologist, he contributed a large number of papers on dermatologic subjects. Among subjects on which he wrote were granuloma inguinale, granuloma annulare, porokeratosis, mycosis fungoides and parapsoriasis. His vast knowledge of general medicine and pathology made him a broad-minded and an extremely well qualified dermatologist. His influence on English dermatology was great.

Sir Malcolm Morris (1847-1924).—Sir Malcolm [7] had his dermatologic training in Berlin and Vienna. He held the position of surgeon to the skin department at St. Mary's Hospital from 1882 to 1902. In 1870 he published a manual of cutaneous diseases, which ran through six editions. He was one of the original members of the London Dermatological Society, which was founded in 1882. With H. S. Brooke, he founded the *British Journal of Dermatology* in 1888 and was joint editor for three years. He was president of the dermatologic section of the Royal Society of London from 1911 to 1913 and president of the section of dermatology and syphilology of the Seventeenth International Congress of Medicine, which meeting corresponded to the International Congress of Dermatology. Dr. Morris was a pioneer in London in the use of radium as a therapeutic agent and was one of the founders of the Radium Institute. He took an active interest in leprosy and was instrumental in the organization and management of a home for lepers. He was interested in public health and published two books on the subject. He also was a contributor to dermatologic literature. I can vouch for the statement that he was a successful teacher, as I attended his clinics at St. Mary's for a year.

J. J. Pringle (1855-1923).—Pringle [7] had his early training in Edinburgh, followed by several years in Paris and Vienna. He was medical registrar in the Middlesex Hospital for two years, beginning in 1885, and then for ten years he served as assistant physician. He served as assistant and later full physician for diseases of the skin until 1920. He was secretary of the London Dermatological Society for sixteen years, beginning in 1884. He was acting editor of the *British Journal*

of Dermatology for five years and secretary to the Third International Congress of Dermatology, held in 1896 in London. He made numerous contributions to dermatologic literature, some of which were monographs; his contributions to the knowledge of adenoma sebaceum, Pringle type angiokeratoma and Pringle seborrheid were outstanding. He edited a pictorial atlas of the skin and Jacobi's dermachromes. He was a corresponding member of several foreign dermatologic societies, including those of France, Vienna, Berlin, Italy and Lisbon. Through his great knowledge he had many followers, and several of his assistants became leaders in dermatology.

Sir Norman Purvis Walker (1862-1943).—He was first assistant and later full physician to the skin department of the Royal Infirmary (Edinburgh). He was lecturer on diseases of the skin in the University of Edinburgh and the School of Medicine of the Royal Colleges of Edinburgh. He translated from the German Hansen and Looft's book on leprosy and Unna's "Histopathology of the Skin." His textbook, "Introduction to Dermatology," went through ten editions. He was a talented teacher. He was not so much interested in rare dermatoses as he was in improving knowledge of common conditions. He was honored by membership in British, French, American and Danish dermatologic societies. He founded the North British Dermatological Society.

Comment.—In 1901 I spent several months attending the clinics of Radcliffe Crocker, Sir James Galloway, Thomas Colcott Fox and J. H. Pringle. This experience was an invaluable one, as all these men were masters in dermatology. They also gave me the privilege of attending meetings of the London Dermatological Society and of the Dermatological Society of Great Britain and Ireland, where a wealth of clinical material was presented and ably discussed. This experience, with a year's training in cutaneous histopathology under J. M. H. MacLeod, gave me an invaluable dermatologic background on which to build a future.

IMPORTANT DERMATOLOGISTS IN THE UNITED STATES

Louis Adolphus Dühring (1845-1913).—Dühring's [8] most important contribution to dermatology was his description of dermatitis herpetiformis. This was done in a series of eighteen papers, written between 1884 and 1891. He was the author of a textbook which went through three editions and was published in Russian, French and Italian. He began a comprehensive work on dermatology, entitled "Cutaneous Medicine"; only two volumes were completed. The material for the

8. Bechet, P. E.: Louis Adolphus Dühring: Great American Dermatologist, Arch. Dermat. & Syph. **30**:367 (Sept.) 1934.

third volume was destroyed by fire, and the work was never taken up again. Dühring was professor of dermatology at the University of Pennsylvania for twenty years but taught dermatology for forty years. His list of publications numbered seventy-eight. He was one of the organizers of the American Dermatological Association and its president twice.

James Clarke White (1833-1916).—White[9] was the first professor of dermatology in the United States. He was a scholar of distinction and had supreme knowledge in chemistry and history. His contributions to dermatologic literature were numerous; probably the most important was a monograph on dermatitis venenata. He first described keratosis follicularis. He also contributed articles on leprosy, angioma serpiginosum and many other diseases. He was one of the founders of the American Dermatological Association and its first president. He also was president of the Sixth International Dermatological Congress in 1907. According to Bechet, he contributed one hundred and twenty-five medical papers, fifty reviews, ninety-four editorials and eight books.

Comment.—The American Dermatological Association was founded in 1876. J. C. White was president; L. A. Dühring and R. W. Taylor, vice presidents; L. D. Bulkley, secretary, and J. N. Hyde, treasurer. The first meeting was held at Niagara Falls in September 1877. Other prominant founding members were G. H. Fox, H. G. Piffard, F. D. Weisse, A. R. Robinson and W. A. Hardaway.

George Henry Fox (1846-1937).—Fox graduated from the University of Pennsylvania in 1869 and spent the three years from 1870 to 1873 studying in Europe. He was elected professor of dermatology in the Columbia University College of Physicians and Surgeons in 1881 and held that position until 1907. He was one of the founders of the American Dermatological Association, of which he was president in 1892 and honorary president in 1926. His interest in dermatologic photography was illustrated by his two atlases of cutaneous diseases, one of which was published in 1880 and the other in 1885. He described match-box dermatitis and a chronic papular disease of the axillas and pubes (Fox-Fordyce disease). He contributed freely to dermatologic literature.

Henry G. Piffard (1842-1910).—Piffard did postgraduate work under Tilbury Fox in London at the same time as did G. H. Fox. They were friends for forty years. Piffard was one of the founders of the New York Dermatological Society and was professor of dermatology in the New York University College of Medicine. He published "Elementary Treatise on Diseases of the Skin" (1876) and "A Treatise on Materia Medica and Therapeutics of the Skin" (1881).

9. Bechet, P. E.: James Clark White, Ann. M. Hist. **7**:503-508, 1935.

James Nevins Hyde (1840-1910).—Hyde was professor of dermatology and syphilology at Rush Medical College from 1873 to 1910. His textbook, published in 1883, went through eight editions. He contributed much in the study of blastomycosis, sporotrichosis and pellagra. He described synovial lesions of the skin and named prurigo nodularis (which was first described by Hardaway under the title multiple itching tumors of the skin). Hyde, with F. H. Montgomery, published a treatise on venereal diseases. He was the author of a large number of publications on dermatologic subjects, and his writings were always up-to-date. He was one of the founders of the American Dermatological Association, of which he was vice president. He was the first to call attention to light as a cause of cutaneous cancer.

W. A. Hardaway (1850-1923).—Hardaway introduced the use of electrolysis for removal of superfluous hair, for which procedure he gave Charles A. Michel credit, as Michel had used electrolysis for removing inverted eyelashes. With Dr. Grindon, he published a "Handbook of Cutaneous Therapeutics" (1907).

Henry W. Stelwagon (1853-1919).—Stelwagon [10] had great ability as a teacher, clinician and writer. His textbook, "A Treatise on Diseases of the Skin," went through nine editions from 1902 to 1919. In 1880 he succeeded Dühring at the Philadelphia Dispensary for Skin Diseases. In 1885 he became instructor in dermatology at the University of Pennsylvania School of Medicine and chief of the dispensary for skin diseases in the Hospital of the University of Pennsylvania. In 1890 he resigned from the University of Pennsylvania School of Medicine and became professor of dermatology at Jefferson Medical College of Philadelphia, which position he held from 1890 to 1918. He was contributor of a large number of articles on dermatologic subjects.

John T. Bowen (1857-1940).—Bowen,[10] an eminent histopathologist, first described the precancerous dermatoses. He also described the epitrichial layer of the epidermis. He was assistant physician and physician in the outpatient department for cutaneous diseases of Massachusetts General Hospital from 1889 to 1914 and was an instructor, assistant professor and professor of dermatology at the Harvard Medical School from 1896 to 1911. He founded the Boston Dermatologic Club (New England Dermatological Society).

John A. Fordyce (1858-1925).—Fordyce [10] described multiple benign cystic epithelioma. This lesion was also described by H. G. Brooke. Fordyce also described pseudocolloid of the lips (Fordyce's

10. Bechet, P. E.: Outline of Achievements of American Dermatology Arranged in Chronological Order, Bull. Hist. Med. **19**:291, 1946: Biographies of Stelwagon, p. 310; Bowen, p. 311; Fordyce, p. 312; Gilchrist, p. 315; Pusey, p. 317; Pollitzer, p. 314; Zeisler, p. 313.

disease), a peculiar disorder of the mucous membrane of the lips and oral cavity. He described the histopathology of chronic itching papular eruption of the axillas and pubes (Fox-Fordyce disease, of which G. H. Fox described the clinical picture). He described infectious eczematoid dermatitis and wrote an early article on allergy, entitled "Influences of Anaphylaxis Reactions" (1911). He was professor of dermatology and syphilology in the Columbia University College of Physicians and Surgeons. For eight years he was editor of the *Journal of Cutaneous and Venereal Diseases.* In 1907 he was secretary general of the Sixth International Congress of Dermatology. He was visiting dermatologist to New York City Hospital for thirty-two years. He contributed to the literature a large number of articles on dermatoses, syphilis and cutaneous histopathology.

T. Caspar Gilchrist (1862-1927).—Gilchrist [10] described cutaneous blastomycosis. He isolated the micro-organism, proved its pathogenicity and accurately described the disease. He was professor of dermatology at Johns Hopkins University School of Medicine and contributed numerous constructive articles to the field of dermatology.

B. R. Schenck.—In 1898, in an article entitled "On Refractory Subcutaneous Abscesses Caused by Fungus Possibly Related to the Sporotrichia," Schenck described sporotrichosis. He worked out its mycology and, by animal experimentations, proved its pathogenicity. Later reports were made by Brayton, Hektoen and Perkins, and by Beurmann in France.

William Allen Pusey (1865-1940).—Pusey [10] did pioneer work in roentgen therapy and, with Eugene W. Caldwell, published a valuable work on the subject, "The Practical Application of Roentgen Rays in Therapeutics and Diagnosis." He was president of the American Dermatological Association, the American Medical Association and the Chicago Medical Society, was one of the founders of the Chicago Dermatological Society and was the author of more than one hundred articles and seven books on dermatologic and allied subjects. His textbook, "The Principles and Practice of Dermatology," passed through four editions. He was editor of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY for a number of years. He first used solid carbon dioxide in the treatment of cutaneous diseases. Other important works are his "History of Dermatology," "The History and Epidemiology of Syphilis," "The Care of the Skin and Hair," and "A Doctor of the 1870's and 1880's." He was professor of dermatology at the University of Illinois College of Medicine from 1893 to 1915 and attending dermatologist to the Cook County Hospital for a number of years. He did much to advance medical education and was a valued colleague and loyal friend.

Sigmund Pollitzer (1859-1937).—Pollitzer [10] was an eminent dermatologist and carried out much investigative work. He was professor of dermatology at the New York Post-Graduate Medical School for twenty years. He was president of the American Dermatological Association and a very active member of the society for forty-one years and was one of the founders of the Section on Dermatology and Syphilology of the American Medical Association. He was the first to describe acanthosis nigricans and hidradenitis destruens suppurativa. He reported the first case of rhinoscleroma to be treated successfully with roentgen radiation; with Unna and Santi, he described parakeratosis variegata. He also contributed much to the modern treatment of syphilis. He wrote seventy-one articles.

Joseph Zeisler (1858-1919).—Dr. Zeisler [10] graduated in Vienna and was in the Vienna General Hospital until 1884, when he came to Chicago. In 1889 he became professor of dermatology at Northwestern University, a position he held until his death. He made contributions on hydroprurigo, dermatitis herpetiformis, pemphigus, angiokeratoma and herpes zoster due to arsenic poisoning, and he wrote several articles on the diagnosis and treatment of syphilis. He brought to Chicago the Vienna school of dermatologic thought, which he had obtained under Kaposi and others. He was an able debater and always courteous to his fellows. He contributed thirty-six articles to dermatologic literature.

Milton B. Hartzell (1859-1927).—Hartzell, a keen observer on dermatologic problems, was professor of dermatology at the University of Pennsylvania School of Medicine. He made important contributions on cutaneous cancer, arsenical keratosis and dermatitis vegetans and was the author of a textbook. He was an expert clinician and pathologist.

Grover Wende (1866-1926).—Wende contributed many articles to dermatologic literature. He first described a form of erythema perstans and clarified the position of dermatitis vegetans. He also first described a form of tuberculosis of the skin under the designation of nodular tuberculosis of the hypodermis. He was a keen clinician and a well qualified pathologist. He served as president and secretary of the American Dermatological Association.

Frank Hugh Montgomery (1862-1908).—Montgomery [10] was associate professor of dermatology in Rush Medical College. He did outstanding work in cutaneous blastomycosis and was co-author with James Nevins Hyde of several editions of a work on diseases of the skin. He was a member of the American Dermatological Association and served as secretary-treasurer. He made a number of contributions to dermatologic literature. He was an excellent teacher and a keen observer, and his clinical descriptions left nothing to be desired. His untimely death was a great loss to the dermatologic world.

SOCIETIES AND ASSOCIATIONS

Dermatologic societies and associations have played an important role in the growth of the subject and in the development of the men participating in their activities. Although European dermatologists were pioneers in the work, the New York Dermatological Society, founded in 1869 by F. D. Weise, H. G. Piffard, Foster Smith and H. W. Bulkley, was the first such group to be established. The Société française de dermatologie et de syphiligraphie was founded in 1889 by E. Besnier, E. Vidal and Fournier. Similar societies have been established all over the world and have achieved brilliant results everywhere. I am personally familiar with the work of the London Dermatological Society, founded in 1882, meetings of which I attended in 1900 and 1901; the American Dermatological Association, founded in 1876, meetings of which I have attended since 1907, and the Chicago Dermatological Society, founded in 1901, meetings of which I have attended since the group's second meeting in that year.

The benefit derived by membership in these societies is incalculable. In the earlier years of these societies, the number of men was limited and the discussions were free. There was an intimate association among the members. As these societies enlarged their membership, the discussions became more formal and much of the former personal intimacy was lost. The number of local, state and national dermatologic societies or associations in the United States and Canada is forty-four.

JOURNALS

Dermatologic journals throughout the world have played a most important part in advancing knowledge in this specialty.

The first English journal was established by Sir Erasmus Wilson in 1867 under the title *The Journal of Cutaneous Medicine and Diseases of the Skin.* The *British Journal of Dermatology* was founded in 1888 by Sir Malcolm Morris and H. G. Brooke.

The first American journal was published during the period from 1870 to 1875, under the title *The American Journal of Syphilography and Dermatology,* with M. H. Henry as editor. In 1875 the *Archives of Dermatology,* edited by L. Duncan Bukley, was established and continued until 1882. In 1883 the *Journal of Cutaneous and Venereal Diseases,* edited by H. G. Piffard and Prince A. Morrow, was first published. This journal has continued until the present date, the title now being THE ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY.

Among numerous foreign journals are the *Archiv für Dermatologie und Syphilis,* founded in 1869 by F. J. Pick and H. Auspitz; *Monatshefte für praktische Dermatologie,* founded by Unna in 1882, and *Annales des maladies de la peau et de la syphilis,* founded in 1843 by P. L. A. Cazenave. The *Annales de dermatologie et de syphiligraphie*

was founded in 1869 by A. Doyon and others; E. Vidal was an early editor. Other German and French journals, together with Italian, Scandinavian and Japanese journals, all have made their contributions.

SPECIAL DISEASE STUDIES

In addition to the discoveries concerning diseases which were described in the biographic sketches, a few others should be mentioned. In the mycotic infection group, the trichophytids were described in 1912 by Jadassohn; observations on the microsporids, dermatophytids and favids were published shortly thereafter.

The important subject of ringworm of the hands and feet was studied in 1892 by Djelaleddin-Mouktar. In 1908 and in 1911 Whitfield studied and reported on 5 and 7 cases, respectively. In 1910 Sabouraud reported on 6 cases of intertriginous eczema (intertrigo), in 4 of which he found Epidermophyton inguinale (tinea cruris). The next study was by Kaufmann Wolfe, in which 25 cases of dyhidrosis were observed. The first comprehensive study in America was made by Ormsby and Mitchell in 1916, when they reported on a group of 65 cases, in all of which fungi were demonstrated. These cases clinically were classed as instances of dyshidrosis, intertriginous eczema and keratoderma.

In 1922 Kummer made a comprehensive report of the various infections produced by yeasts and yeastlike organisms. These diseases now include erosio interdigitalis blastomycetica, "water bed" mycosis, mycotic paronychia, mycotic intertriginous dermatitis and some cases of perlèche.

Much additional information has been recorded on the cutaneous manifestations of leukemia, pseudoleukemia and other members of the lymphoblastoma group. In leprosy, two important types have been described: the tuberculoid and the lazarine. In therapy, the gold and bismuth preparations have revolutionized the treatment of lupus erythematosus.

Avitaminosis.—Vitamins have been recognized for more than thirty years, and since they have been isolated in pure form they have become important in solving some problems in etiology and treatment of several diseases, including some of the dermatoses. "Vitamins" was a term applied by Funk in 1912 to a group of nutritional substances called by Hopkins accessory factors. These substances are required by the animal organism in addition to carbohydrates, fats, proteins, salts and water. Vitamins are organic compounds required for the normal growth and maintenance of life of animals and man.

Avitaminosis is due to inadequate utilization of vital substances contained in food. This ordinarily occurs through an unbalanced diet, in which some necessary foods have not been consumed. It may

occur, however, when the food supply is adequate. According to Rhoads, the latter situation may be due to loss of vitamins through diarrhea, inability of the intestinal tract to absorb normally the essential dietary constituents, lack of a bodily factor required to convert vitamins into a usable form, a high individual vitamin requirement and/or the inhibition, through infection, of the function of vitamins.

The chief diseases caused by vitamin deficiencies are pellagra, beriberi, scurvy (scorbutus) and rickets. Among dermatoses are Darier's disease (keratosis follicularis), pityriasis rubra pilaris and, possibly, keratosis pilaris, lichen pilaris seu spinulosis (Crocker) and xerosis.

Vitamin A is an important factor in the metabolism of epithelial structures, both in the skin and in the mucous membranes. The syndrome of night blindness, keratomalacia and a follicular keratosis is the result of vitamin A deficiency and clears up with the use therapeutically of this vitamin. Vitamin A is also valuable in the treatment of the hyperkeratotic diseases previously mentioned.

Thiamine chloride (vitamin B_1) is of value in preventing and correcting beriberi. A condition described by Sebrell and Butler under the designation cheilosis is an example of riboflavin deficiency. In it a perlèche-like condition exists at the angles of the eyes; the tongue presents a magenta color; there may be a vascularizing keratitis; conjunctivitis is simulated, and corneal opacities, mydriasis and iritis occur. Keratitis rosacea also appears to be a riboflavin deficiency and is usually benefited by administration of this substance.

The results of the use of ascorbic acid (vitamin C) in treatment of scurvy are often spectacular. Ascorbic acid also promotes wound healing and is used as a preventive of untoward reactions to arsphenamine, gold compounds and the sulfonamide drugs.

Pellagra was first demonstrated to be a dietary deficiency by Goldberg and associates, of the United States Public Health Service. Their work was epoch making, as it cleared the way for the successful management of a serious prevalent disease which was a scourge in the southern states. Nicotinic acid is practically specific in its treatment, though riboflavin and other vitamins, together with food rich in pellagra-preventive vitamins, are useful. A preparation of vitamin D_2 (drisdol®) has been found useful in the treatment of tuberculosis luposa (lupus vulgaris).

There is no doubt about the value of vitamins when used under proper supervision nor is there any doubt that vitamin therapy has been gravely overdone by the unlimited use of these substances by the laity, with no supervision. Much more could be said on this important subject, but time and space are limited.

Anaphylaxis and Allergy.—The development of knowledge of anaphylaxis and allergy gave valuable information as to the cause, the

diagnosis and the treatment of many diseases, including several important dermatoses. The terms anaphylaxis and allergy are used to designate hypersensitiveness of animals and man to various substances, such as animal and vegetable proteins, drugs and physical agents. Idiosyncrasy is the old term for hypersensitiveness to drugs. Hypersensitiveness to various foods in some persons has long been recognized, without adequate explanation as to the cause.

The term anaphylaxis was employed by Richet to describe certain phenomena induced in animals on a second injection of substances that were harmless on the first injection. Allergy was the term employed by Pirquet (1903) to denote an altered reactivity observed clinically in patients given injections of serum. Most observers agree that anaphylaxis is a true antigen-antibody reaction, and some think the term should be reserved for this type of reaction only. Allergy covers a larger field and includes not only anaphylaxis but other phenomena induced by altered reactivity.

Through the work of a large number of investigators, the subject of allergy has grown to the extent of being considered a medical specialty. In 1903, Theobald Smith noted that guinea pigs used in the standardizing of diphtheria antitoxin often died after a second injection. It was soon learned that these reactions were anaphylactic, due to the serum employed and not to the toxic content. To obviate this reaction in human beings, prophylactic injections of the toxin were made with beef serum so as to avoid sensitization to horse serum, the vehicle employed in diphtheria antitoxin therapy. Hypersensitiveness to drugs is common. Urticaria and erythema are the commonest forms of reaction, though practically all the lesions seen on the skin may be produced by drugs.

Allergy to animal and plant substances is seen in persons who react to hair and dandruff of animals; to feathers of chickens, ducks and geese and to various plants, such as rhus and primrose. Allergy to animal substances is frequently manifested as asthma, hay fever or vasomotor rhinitis. Occasionally a dermatitis is produced.

Contact with ivy, primrose, oak and other plants results in a dermatitis only in skins sensitized to these substances. Ragweed is a common cause of eczematous dermatitis and of hay fever in sensitive subjects.

There are two methods of cutaneous testing for allergic sensitization: the cutaneous, or scratch, method and the intradermal. Tests are made in the former by applying the foreign material in powder form to a scratched area on the skin. On this material is placed 1 drop of a 0.1 normal solution of sodium hydroxide, after which procedure the mixture is gently rubbed in. A positive reaction is indicated by the formation of an urticarial wheal of irregular outline, surrounded by a zone of erythema. In the second method, the materials are prepared in solution and injected intracutaneously. A positive reaction

presents the same signs as are seen with the scratch method. Controls are used. When the reaction is positive, the lesion is fully developed in from fifteen to thirty minutes.

Hypersensitiveness to certain foods is relatively common. A predisposition to acquire this condition is often inherited. The commonest allergens for infants are cow's milk, eggs, potato, oatmeal, rice, peas, chicken and beef juice. For adults, the commonest offenders are seafoods, fruits (particularly strawberries), buckwheat, pork and cheese. Cutaneous tests may be employed to detect the food containing the sensitizing protein.

That allergy to food exists there appears to be no doubt, and that this condition is an etiologic factor in a certain proportion of cases of eczema, urticaria, angioneurotic edema, varieties of the erythemas and probably some other dermatoses seems likely. Bacterial sensitization explains the occurrence of tuberculids. Mycotic sensitization explains that of the trichophytids, microsporids and favids.

Duke described a group of patients with physical allergy who presented symptoms of asthma, vasomotor rhinitis, conjunctivitis, photophobia, abdominal pain, erythema, pruritus, urticaria, angioneurotic edema, eczema and shock caused by light, heat, cold, mechanical irritation, freezing and burns.

THERAPEUTIC METHODS

SULFONAMIDE COMPOUNDS

Employment of the sulfonamide group of drugs[11] represents an achievement in the treatment of several important diseases, including dermatoses.

Sulfanilamide was first synthesized in 1908 by a German organic chemist. The development of the numerous modifications has occurred in France, England and this country. An early and important report was made in this country by Perrin H. Long and Eleanor A. Bliss. It was soon found that these drugs produced a profound effect on streptococcic and other infections. They have been used successfully in treatment of chancroid lymphogranuloma venereum, erysipelas, cellulitis, erysipeloid, hidradenitis suppurativa, lymphangitis, pyoderma gangrenosum and chronic streptococcic ulcers. Impetigo responded well to local applications of sulfathiazole, but use of this drug was soon abandoned in treatment of that disease on account of its sensitizing effect. Sulfapyridine N.F. is of much value in treatment of dermatitis herpetiformis. While extremely valuable therapeutically, these

11. Sulfanilamide Compounds, in Ormsby, O., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 93 (bibliography). Spink, W. W.: Sulfanilamide and Related Compounds in General Practice, Chicago, The Year Book Publishers, Inc., 1943 (bibliography).

drugs are not devoid of danger, as severe toxic reactions, both general and cutaneous, not infrequently occur.

ANTIBIOTIC SUBSTANCES

During the past few years a large number of antibiotic agents have been developed, some of which have been used extensively with success. The chief members of this group are penicillin, streptomycin and tyrothricin. Penicillin was discovered by Fleming in 1929. It is the most important member of the antibiotic group. Its use in syphilis has been extensive and highly successful.

Penicillin.—Penicillin [12] is given by injection, by mouth and in local applications. It is of value in treatment of impetigo, ecthyma and secondary pyodermas and of great value in treatment of erysipelas, cellulitis, erysipeloid, anthrax, carbunculosis and furunculosis. In cases of Vincent's angina 250 to 500 units is applied locally four times daily with success. A convenient method of giving an adequate dose consists in the intramuscular injection of 300,000 units of calcium penicillin per cubic centimeter suspended in peanut oil containing 4.8 per cent white wax U. S. P. (penicillin injection in oil and wax U. S. P.). This preparation does not produce tumors, such as those which were produced by injections of paraffin. Reactions to penicillin consist chiefly of urticaria and angioneurotic edema.

Tyrothricin.—This agent,[12] derived from the soil bacillus Bacillus brevis, contains gramicidin and tyrocidin. It is used only in local applications and cannot be incorporated into ointments or taken internally. It is valuable in the treatment of sycosis, impetigo, ecthyma, ulcers, furuncles, carbuncles and axillary abscesses.

Streptomycin.—This substance,[12] prepared from a strain of Actinomyces (Streptomyces) griseus, shows promise in the treatment of tuberculosis. It is also valuable in the treatment of tularemia.

BACTERICIDAL CHEMICALS

Nitrofurazone.—This compound [13] (furacin® [5-nitro-2-furaldehyde semicarbazone]) is an excellent bactericidal agent. It is derived from pentose found in oat hull. It is most efficient in 0.2 per cent solution in a greaseless, water-miscible base of polyethylene glycol, 75 per cent, and propylene glycol N.F., 25 per cent. It is nonirritating, easy to apply and valuable in the treatment of superficial infections of the skin and

12. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1946: Penicillin, pp. 1-258; Tyrothricin, p. 267; Streptomycin, p. 313.

13. Downing, J. G.; Hanson, M. C., and Lamb, M.: Use of 5-Nitro-2-Furaldehyde Semicarbazone in Dermatology, J. A. M. A. **133**:299 (Feb. 1) 1947.

acute folliculitis. Pyodermas implanted on a dermatosis or ulcer respond well to nitrofurazone therapy. The chemical has a tendency to sensitize the skin, but this effect is not important.

BAL (British antilewisite).—BAL [14] is a remarkable therapeutic agent for intoxications from heavy metals (arsenic, bismuth and mercury). It is given by intramuscular injection in the dose of 2.5 to 3 mg. per kilogram of body weight, with use of a 10 per cent solution of BAL and a 10 per cent solution of benzyl benzoate in peanut oil. Injections are repeated every four hours for two days, every six hours the third day and twice daily for six additional days. Spectacular results have been obtained in treatment of pericapillary encephalorrhagia (hemorrhagic encephalitis), dermatitis exfoliativa and other untoward reactions to arsenicals.

FUNGICIDES

Undecylenic Acid.—This fungicide [15] is recommended in the treatment of ringworm. Shapiro and Rothman [16] recommended the following ointment (zincundecate [desenex®]): undecylenic acid, 5 per cent, and zinc undeclyenate, 20 per cent, in vanishing cream (p_H 6.5). Undecylenic acid is also used in powder form. It is a potent fungicide and not irritating to the skin.

Tripelennamine Hydrochloride.—This drug [17] (pyribenzamine hydrochloride®; N,N-dimethyl-N′-benzyl-N′-[α-pyridyl] ethylenediamine hydrochloride) is an excellent antianaphylactic and antihistamine compound and is not toxic to any degree. It is valuable in treatment of urticaria, both acute and chronic. It is useful in relieving the pruritus of atopic dermatitis. It is of considerable value in treatment of dermatitis herpetiformis. It is also effective in combating physical allergy. Toxic reactions are mild and do not interdict its use over long periods when necessary.

Diphenhydramine Hydrochloride.—This compound (benadryl hydrochloride® [beta-dimethylaminoethylbenzohydryl ether hydrochloride]) [18]

14. B. A. L., in Sulzberger, M. B.: Yearbook of Dermatology and Syphilology, 1946, Chicago, The Year Book Publishers, Inc., 1947, pp. 72-82 (articles by several authors reporting on treatment).

15. Hopkins, J. G., and others: Fungistatic Agents for Treatment of Dermatophytosis, J. Invest. Dermat. **7**:239, 1946.

16. Shapiro, A. L., and Rothman, S.: Undecylenic Acid in the Treatment of Dermatomycosis, Arch. Dermat. & Syph. **52**:166 (Sept.) 1945.

17. Osborne, E. D.; Jordan, J. W., and Rausch, N. G.: Clinical Use of New Antihistaminic Compound (Pyribenzamine) in Certain Cutaneous Disorders, Arch. Dermat. & Syph. **55**:309 (March) 1947 (bibliography).

18. Lynch, F. W.: Benadryl in Dermatologic Practice, Arch. Dermat. & Syph. **55**:101 (Jan.) 1947. (Literature.)

is valuable in the treatment of urticaria, both acute and chronic. It is very effective in relieving urticaria due to drugs. It also is of benefit in some cases of pruritus, both general and local (pruritus vulvae). It has been of considerable value in some cases of erythema multiforme. It produces toxic reactions of varying degrees but not of sufficient severity to interdict its use. Its dosage is from 50 to 150 mg. daily.

PHYSICAL AGENTS

Roentgen Rays.—This physical agent was discovered in 1895 by W. C. Roentgen, a physicist. He made this discovery as the result of investigations of the behavior of high potential electricity in a rarefied atmosphere. The radiation has been used as a therapeutic agent since 1898. Notable work in connection with its use has been done in this country by William Allen Pusey and George M. MacKee. The use of roentgen radiation in hypertrichosis has long since been abandoned. This therapeutic measure is very valuable in the treatment of basal cell epithelioma, keloid, acne, tinea capitis (ringworm of the scalp), indurated eczemas and several other diseases.

Radium.—This element [19] was discovered by Marie Curie in 1898. Radium therapy began in 1901. Radium is of value in the treatment of basal cell epithelioma, hemangioma and other types of nevi. Wickham and Degrais, in Paris, and Howard Kelly, of Johns Hopkins University, did much pioneer work in developing the use of radium as a therapeutic agent.

Other physical agents include liquid air, discovered in 1899, and solid carbon dioxide, introduced in 1907. W. A. Pusey first recommended solid carbon dioxide, and it has since superseded liquid air on account of its availability and because of the fact that the agent can be molded to fit exactly the lesion treated. Moles and other nevi, including small hemangiomas and small epitheliomas, are successfully treated by these agents.

SUMMARY

In this paper are presented brief biographies of a few outstanding dermatologists in Austria, Germany, France, Italy, Scandinavia and the United States, and a summary of discoveries of therapeutic measures, some of them remarkable. The development of dermatologic knowledge during the last decade has been extraordinary. The promise of a brighter future is excellent, owing to better equipment and the large number of exceptionally well qualified men to carry on the work.

55 East Washington Street (2).

19. Montgomery, H.; MacKee, G. M., and Cipollaro, A.: X-Rays and Radium in the Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1946.

EXTENSIVE BLUE PATCHLIKE PIGMENTATION

A Morphologic Variant of Blue Nevus? Persistent Extrasacral Mongolian Blue Spot? Diffuse Mesodermal Pigmentation?

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THE BLUE nevus, a usually benign lesion, has received increasing attention since Tièche [1] originally described it, in 1906, as benign melanoma. Special attention to this entity in this country was slight until 1939, when Montgomery and Kahler [2] published their complete review of this subject. Since there is little to be gained by resurvey of the literature, we suggest that if histologic criteria are diagnostic of blue nevus, our clinical concept of this condition would seem to require enlargement to include variants of the original description. The literature indicates that such thinking has already occurred, but has not been emphasized sufficiently. Tièche's comparison of blue nevus and Mongolian blue spot as well as more recent reports describing extensive plaquelike blue nevus are in point.

Before describing this morphologic variant of which we believe our case is a good example, we shall summarize briefly the generally accepted clinical and pathologic concepts of blue nevus and its relationship to Mongolian blue spot, especially the ectopic (extrasacral) and adult types. Tièche, in his original review described minutely the essential features of blue nevus. The only significant contribution to the pathogenesis of blue nevus in recent years is Sato's demonstration [3] that the pigment cells are dopa positive (melanoblasts) and are identical with the cells of Mongolian blue spot.

For the sake of brevity, we cite the condensed clinical and histologic description of blue nevus compiled by Montgomery and Kahler.

The blue nevus is a sharply circumscribed, round or oval slightly elevated papule or nodule varying from 2 to 15 mm. in diameter, rarely exceeding the

1. Tièche, M.: Ueber benigne Melanome ("Chromatophorome") der Haut, "blaue Naevi," Virchows Arch. f. path. Anat. **186**:212-229, 1906.

2. Montgomery, H., and Kahler, J. E.: The Blue Nevus (Jadassohn-Tièche): Its Distinction from the Ordinary Moles and Malignant Melanomas, Am. J. Cancer **36**:527-539, 1939.

3. Sato, K.: Bertrag zur Kenntnis des "blauen Nävus," Dermat. Wchnschr. **73**:1073-1077, 1921.

latter size. The majority of the lesions are rather firm to palpation and present a definite degree of induration. The characteristic feature is the color. In 52 per cent of the lesions in the present series, the color was described as blue or mottled blue; in 32 per cent, as blue-black; in 8 per cent as blue-gray; in 5 per cent, as steel blue; and in 3 per cent, as black. A tumor which is deep blue, blue-black, or even blue-gray in color, taken together with a history of onset shortly after birth without subsequent increase in size of the lesion, usually permits a definite clinical diagnosis of blue nevus. When, however, the lesion is steel blue or black, histopathologic studies may be necessary to differentiate it from a malignant melanoma.

Histologically, the typical blue nevus is composed of spindle-shaped melanoblasts grouped in irregular masses in the lower two-thirds of the cutis. The epidermis varies in the amount of pigment present, but ordinarily does not reveal an increase in pigmentation. There may be a decrease in the pigment in the epidermis directly over the tumor.

The greatly elongated tumor cells are thickest at the center and gradually taper at each end to a fine point. They have very long wavy bipolar processes. Some seem to have branching or dendritic processes. The cytoplasm is filled with a dark brown pigment occurring in fine granules distributed evenly throughout the cell. When the cells are seen in cross-section, the nucleus may be surrounded by a clear halo, the pigment occupying a peripheral rim of the cytoplasm. The centrally located nucleus is oval, its chromatin equally distributed except for an eccentrically placed nucleolus. The tumor cells are irregularly grouped into bundles which may be small and scattered throughout the lower cutis and even extend into the sub-cutis, or may be consolidated into one or more large masses. The cells tend to group themselves about sweat ducts, sweat glands, cutaneous nerves and blood vessels, and less frequently about hair follicles. Not all the cells of the individual tumor contain pigment; however, many apparently nonpigmented cells in a section stained with hematoxylin and eosin will show definite pigment granules on impregnation with silver nitrate. The pigment contained in these cells is melanin, as demonstrated by the fact that it darkens with silver, bleaches with hydrogen dioxide, and does not give a positive reaction for iron.

The typically elongated spindle-shaped cells of the blue nevus with their long bipolar or dendritic processes, are readily distinguished from the ordinary oval nevus cell. Even when seen in cross-section, they may be differentiated from the nevus cell by their smaller size and absence of arrangement in columns, nests, or alveoli.

In Mongolian blue spot, just as in blue nevus, the pigment cells lie in the lower two thirds of the corium. Occasional examples show these cells extending up to the papillary body and as deeply as to the subcutis. The papillary body and the pars reticularis usually remain free of them.

Numerous examples of Mongolian blue spot, often extrasacral in location, persisting to adult life, have appeared in the literature. As long ago as 1887 Sekiba[4] observed 2 cases in adults. Other per-

4. Sekiba: On the Bluish Black Spots, J. Anthrop. Soc. Tokio **3**:68, 1887.

sistent adult cases were reported by Leven,[5] Jamamoto,[6] Narducci[7] and Fisher and Yü (children up to 14 years of age).[8]

Specifically, reports of blue lesions (nevi) involving the face, such as in our patient, have more recently appeared. Ebert[9] described an eruption occurring in a 23 year old woman who noted pigmentation for the first time on the sclera of her left eye eight years previously. Five years later pigmentation first appeared on the left temple and spread slowly since that time. The history gave no clue as to diagnosis.

Examination revealed a bluish black pigmentation of the lower half of the sclera of the left eye. It was sharply marginated where it stopped, about 1 mm. from the cornea. The right eye had a similar but lighter and less extensive pigmentation, beginning at the inner margin near the cornea but separated by an unpigmented space. The skin about the region of the left temple and left eyelid was the site of a bluish gray slightly mottled pigmentation, with rather definite margins, about 8 by 10 cm.

Biopsy of the pigmented region of the temple showed no change in the epidermis and no increase in epidermal pigmentation. There was increased pigmentation in the middle portion of the cutis. It consisted of elongated cells ranged parallel to the surface and containing large brown pigment granules. There were a few pigment-bearing cells in the upper part of the cutis.

From the location and the nature of the lesion, and the reaction to staining with polychrome methylene blue (methylthionine chloride U.S.P.), the pigment was apparently melanin. In the discussion Becker agreed that the diagnosis was blue nevus histologically. He expressed the opinion that the cells were too deep to be simply pigment-carrying cells (melanophores). Ebert expressed the opinion that before a final diagnosis could be made biopsy should be performed to determine

5. Leven: Zur Frage des Mongolenflecks, Deutsche med. Wchnschr. **48**:231-232, 1922.

6. Jamamoto: Ueber Mongolenflecke und hellblauen "mongoloiden" Nævus, Arch. f. Dermat. u. Syph. **149**:344-348, 1925.

7. Narducci, F.: (*a*) Sul neo leucopigmentario e sulla vitiligine perinevica, Arch. ital. di dermat., sif. **1**:271-275, 1925; (*b*) Sulle chiazze mongoliche, Gior. ital. di dermat. e sif. **67**:1476-1479, 1926.

8. Fischer, W., and Yü, S. C.: Kurzer Beitrag sur Kenntnis des Mongolenflecks, Arch. f. Schiffs- u. Tropen-Hyg. **23**:447-450, 1919. Among others, F. R. Bettley (Brit. J. Dermat. **50**:181-187, 1938) and C. L. Collins (Proc. Roy. Soc.) *Med.* **40**:505-506, 1947) have reported pigmented patches on the shoulder and neck appearing in adult life. The histologic appearance of the cutaneous lesions in both of these cases was similar to that of our case. Collins classed his case as "Blue Naevus in a Mongolian Patch," while Bettley called his "Progressive Melanosis of the Skin."

9. Ebert, M. H.: Mongolian Spots, Arch. Dermat. & Syph. **17**:256-257 (Feb.) 1928.

whether the deep cells were melanoblasts or simple pigment-carrying cells. No examination was made for metallic deposits.

Cornell [10] reported a similar case with the diagnostic possibilities of blue nevus or argyria. This eruption occurred in a 28 year old woman who presented a discoloration on the right side of her face. The patient stated that at the age of 16 she observed a bluish discoloration of the sclera, which had gradually become worse in the succeeding twelve years. At the age of 25, she began to notice a bluish discoloration on the forehead and below the right eye. Prior to the onset of the discoloration she had been struck in the right eye. There was no history of silver medication externally or internally. There was a bluish black pigmentation under both eyes, especially the right one, on the right side of the forehead and on the right eyeball. There was also bluish discoloration of the sclera of the right eye and of the right intraorbital area.

Abramowitz and Tauber, in discussion of this case, stated the belief that it was a blue nevus. Niles stated that one objection to the diagnosis of blue nevus was that the condition was not unilateral and that the symmetry of the eruption might point to some other causative possibility. Unfortunately, no histologic examination was reported.

O'Leary, Montgomery and Brunsting [11] presented a patient with a disease under the title of benign melanosis or metallic pigmentation. This eruption occurred in a 25 year old woman who noticed a blue spot on the left temple at the age of 17. Since then, there was a gradual extension to the eyelids and eyeball. She had been treated with ultraviolet rays and some "bleaching packs." Silver nitrate had not been used in the eyes, although the throat had been painted with it twice. No occupational factors were elicited.

On examination, the patient presented a bluish pigmentation of the left temple, eyelid and eyeball. The left cheek was depressed, but no hemiatrophy was present. The lesion stopped at the hair line, and the eyebrow was not involved. On ophthalmoscopic examination, the bulbar conjunctiva showed no involvement and the cornea was clear. There was a velvety dark brown appearance of the whole left iris except for a sector 3 to 4 mm. wide at 6 o'clock.

Histologic examination showed increased melanin pigmentation, at first glance resembling that of blue nevus with numerous dendrite-like cells in the upper portion of the cutis. Dark field examination revealed much of this pigmentation to be highly refractile and indicated the presence of some type of heavy metal. The granules were not as fine

10. Cornell, V. A. H.: A Case for Diagnosis (Blue Nevus? Argyria?), Arch. Dermat. & Syph. **36**:1261-1262 (Dec.) 1937.

11. O'Leary, P. A.; Montgomery, H., and Brunsting, L. A.: Benign Melanosis: Metallic Pigmentation? Arch. Dermat. & Syph. **31**:411-412 (March) 1935.

as silver granules, nor was there any deposit in the propria of the sweat glands or in the sweat ducts, as in a case of pigmentation supposedly due to cold cream previously observed. Some of these refractile particles seemed to parallel or merge with elastic fibers, but they were much too fine for the ordinary deposits of mercury. It was felt that it was not a blue nevus or argyria. A microscopic diagnosis was made of heavy metal pigmentation plus increased melanin pigmentation.

In the discussion, Sweitzer stated that the lesion looked more like blue nevus than metallic deposits. O'Leary stated that the demonstration by dark field examination of what was interpreted as heavy metal has confused the diagnosis which was formerly thought to be blue nevus.

Montgomery and Kahler [2] suggested that these plaquelike blue pigmented areas may represent aberrant and persistent Mongolian spots, and commented that they do not represent the usual clinical picture of the blue nevus.

Upshaw, Ghormley and Montgomery [12] called attention to one type of clinical variant of the blue nevus consisting of an irregular linear lesion 3 to 6 cm. in width, which extended from the lower part of the sternum laterally to the left midaxillary line. The lesion was composed of multiple firm dark blue round nodules which were slightly raised above the surrounding skin. There also was a bluish discoloration of the skin in the intervening small areas between the circumscribed nodules. The original clinical impression was that of vascular nevus. The histologic picture was that of a blue nevus.

We are aware of the fact that several patients have been reported with cutaneous lesions essentially similar to those of our patient, but which, because of associated phenomena, may have had some relationship to von Recklinghausen's disease. For example, Pack and Livingston [13] cited the case of a patient whose back was covered by a congenital blue nevus. This patient also had von Recklinghausen's disease, and a malignant melanoma subsequently developed in the interscapular area and metastasized to the lungs and brain. More recently Carleton and Biggs,[14] under the title, "Diffuse Mesodermal Pigmentation with Congenital Cranial Abnormality," described the case of a 14 year old healthy girl whose skin was covered with profuse bluish bruiselike spots, especially numerous on the upper part of the trunk, behind the ears and in the margin of the forehead. She also had blue spots on the nose and lips, the vestibule of the mouth and the iris and sclera, par-

12. Upshaw, B. Y.: Ghormley, R. K., and Montgomery, H.: Extensive Blue Nevus of Jadassohn-Tièche, Surgery **22**:761-765, 1947.

13. Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 3, p. 2077.

14. Carleton, A., and Biggs, R.: Diffuse Mesodermal Pigmentation with Congenital Cranial Abnormality, Brit. J. Dermat. **60**:10-13, 1948.

ticularly the left. There had been a progressive increase since birth, but a considerable increase in number occurred at about the age of 9. There was a bossy thickening of the skull behind the ears, and a roentgenogram of the skull showed pronounced ballooning of the posterior cranial fossa, forming an unusual picture. Histologically the cutaneous lesions were essentially like those in our patient, consisting of a widespread infiltration of dendritic or bipolar cells containing fine brown pigment granules which gave the histochemical reaction of melanin. These cells congregated around blood vessels and sweat ducts, and, in addition, they were scattered through the dermis, among the collagen

Fig. 1.—Side view of the patient reported on showing pigmentation on the forehead and the cheek.

fibers. There was no tendency to circumscription as in blue nevus, although the pigment cells were more numerous in the deep than in the superficial part of the dermis. The cells were dopa positive. Parkes Weber expressed the opinion that the condition in this patient might represent a "forme fruste" of von Recklinghausen's disease, in which the sole manifestation is an abnormality of pigmentation. After consideration of the possibility of blue nevus or Mongolian blue spot in this case, the authors suggested "that this case represents a diffuse abnormality in mesodermal pigmentation, not exactly comparable with any hitherto described condition and associated with an unusual cranial anomaly." We believe, in spite of the arguments advanced against it,

that the condition in this patient was an unusual variant of blue nevus or persistent Mongolian blue spots similar to that in our patient.

To this expanding concept of clinical variants of possible blue nevus, we wish to add our observations on a case similar in clinical appearance to those described by Ebert, Cornell, O'Leary and his collaborators, and, from the point of view of the skin, with that of Carleton and Biggs. In our case spectroscopic examination revealed no metallic deposits. Slit lamp examination failed to reveal silver deposits in the cornea or sclera. The history and the histologic examination rule out malignancy. Histologic observations, however, indicate that the disease in this case falls into the category of blue nevus or Mongolian spot. Dr. Ketron first suggested the clinical diagnosis of blue nevus in our case.

Fig. 2.—Low power photomicrograph illustrating the band of pigment-containing cells concentrated around the hair structure (× 200).

REPORT OF A CASE

A white woman of 34 years was first seen by one of us (H.P.) on March 5, 1947 (fig. 1). She stated that she first noticed pigmentation on the right side of the forehead at about the age of 20. During the succeeding few years, after onset, the eruption spread to the left side of the forehead. At about the same time she noticed "bluish circles" around the cornea of both eyes. Early in 1946, the process spread down both cheeks and some mottled pigmentation appeared on the left forearm. Sunlight had no effect on the intensity of pigmentation. She denied contacts with silver salts except that some argyrol® (a silver vitellin preparation) was instilled into the eyes three times after the condition had been present for about eight or nine years. A careful history

of all preparations ingested and used locally was obtained without any significant help as to diagnosis. The patient was rather intelligent, and the history obtained was reliable.

Examination revealed a deep blue pigmented roughly symmetric patch on the forehead. This patch was particularly dark on the sides of the forehead and on the right side extended into the scalp. In the center of the forehead, pigmentation dipped down between the eyebrows to the upper part of the nose. There was a rather faint extension onto the cheeks. The border was sharply demarcated and not indurated. Around the cornea of both eyes, extending about 0.2 cm., there was a band of sharply limited bluish pigmentation of the sclera. Slit lamp examination showed no evidence of silver deposit. Spectroscopic examination revealed no silver or other metal.

Fig. 3.—High power photomicrograph of elongated spindle-shaped pigment-containing cells (× 2,000).

A biopsy specimen from the forehead revealed (H. B.) that the epidermis was thin, with keratinous plugs here and there; otherwise there was scanty hyperkératosis. The corium contained condensed collagen with a suggestion of elastic tissue degeneration. There were foci of inflammatory cells. The hairs, sweat apparatus and fat were normal. The chief feature of this section was a band of spindle cells filled with brown pigment, with their axis parallel to the cutaneous surface lying in the middle part of the cutis, mostly above the level of the sweat glands and below the pars papillaris (figs. 2 and 3). The pigment was brown and coarse and did not give the staining reaction of iron. There was definite concentration of pigment around the hair follicles. Contrary to the usual picture of blue nevus, there was no disruption of the structure of the collagen. This was more in keeping with the histologic appearances of

Mongolian blue spot, although this picture cannot be used as an absolute criterion of differentiation between these two conditions.

COMMENT

The condition in this case departs from the original clinical description of Tièche in three distinct ways. First, the lesion was a bluish nonindurated patch involving an extensive area of the forehead, scalp, face and sclera. Secondly, it did not appear at birth or during childhood. Thirdly, there was an extension of the process with age in contrast to the original description that the lesions remain static. Objectively this bluish pigmentation resembled more the clinical description of extrasacral Mongolian spot than blue nevus. It differed in its course from the usual evolution of extrasacral Mongolian spot in that it increased in intensity with age and appeared for the first time in adult life.

Because of the strikingly similar histologic picture of blue nevus, Mongolian spot and the variant herein described, it is suggested that they all be included in the concept of a single clinical entity. In order to avoid introduction of any new terminology, the name blue nevus seems most appropriate for this entity, particularly since the Mongolian spot can occur in the non-Mongolian races and the term fails to convey any indication of the nevoid origin or clinical appearance of the lesion.

SUMMARY

The original concept of blue nevus as described by Tièche, and later by European and American authors, is that of a circumscribed lesion which fundamentally is identical histologically with Mongolian blue spot. We have described a morphologic variant involving the face of a woman, which appeared after birth and which clinically resembled Mongolian blue spot more than it did the common concept of blue nevus, in that it was extensive and nonelevated. The facial localization of this process in our case is not unique, nor is the fact that it did not appear during childhood, as in the so-called persistent Mongolian blue spot. Because of the close histologic similarity, it is suggested that these morphologic variants of bluish pigmentation be included in one clinical concept.

Dr. James W. Anderson, of Norfolk, Va., gave technical assistance and Mr. Wardlaw M. Hammond, Philadelphia, made the photomicrographs.

STEROID HORMONES

Their Fungistatic and Genestatic Effect on Pathogenic Fungi

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THE ROLE of steroid hormones in relation to immunity has recently aroused the attention of numerous biologists. While it is admitted that genetic, cellular, nutritional and environmental factors contribute to this rather complex mechanism, it has been demonstrated by White [1] that the cortex of adrenals also plays an important part in the development of immunity. Since the activity of the adrenals is dependent on pituitary adrenotrophin secretion, it is well conceivable that estrogens, by influencing the pituitary adrenotrophic hormones, are indirectly associated with certain phases of immunity. According to White ". . . . it is not unlikely that sex differences in immunity, both natural and experimentally produced, may be related in part to the diverse action of estrogens and androgens in influencing the level of pituitary adrenal cortical secretion."

As a consequence, the endocrine response to a particular stress may affect many diverse physiologic processes which contribute to the immunity of the organism. MacKenna,[2] in a recent article emphasized that in relation to superficial fungous infections "there is the influence of sex on many forms of the malady" and, furthermore, that in his experience "tinea of the glabrous skin is much less common in adult females than in man."

It appears unnecessary to enter into a discussion of the well known fact that microsporon infections of the scalp disappear, as a rule, almost spontaneously with the onset of puberty. It may, however, be of interest in this connection to mention that Beck,[3] among the same number of tuberculous patients during a period of two and a half years, found only 2 women affected with erythrasma, whereas

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1. White, A.: Relation of the Adrenals to Immunity, Bull. New York Acad. Med. **24**:26, 1948.

2. MacKenna, R. M. B.: Dermatology: An International Outlook, J. A. M. A. **135**:1128 (Dec. 27) 1947.

3. Cited by Pochlmann, A.: Erythrasma, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 11, p. 714.

39 men were affected by the malady. It is furthermore of interest that Emmons and his co-workers,[4] in the series of cases investigated, found that the incidence of positive reactions to histoplasmin and blastomycin is twice as high in male as in female patients.

A similar sex difference in relation to histoplasmin sensitivity has been reported by Prior,[5] who found that the "reaction rates for males are from 1-16 per cent greater than those for females." It may be of added interest to mention that experimental sporotrichosis is far

Fungistatic Effect of Hormones on Pathog

	Concentration	Alpha Estradiol	Estradiol Benzoate	Ethynil Estradiol	Estrone	Progester
Microsporon audouini	A	70.8 ± 6.1	92.1 ± 0.5	21.4 ± 1.5	69.4 ± 3.7	37.1 ± 4
	B	88.6 ± 4.4	94.7 ± 1.6	71.1 ± 4.3	86.4 ± 0.4	68.0 ± 3
Microsporon lanosum	A	8.6 ± 5.2	88.3 ± 0.7	21.7 ± 17.3	79.2 ± 0.5	64.0 ± 3
	B	73.3 ± 3.3	95.7 ± 1.3	84.6 ± 2.1	90.7 ± 3.8	92.2 ± 1
Microsporon fulvum	A	63.3 ± 0.4	98.3 ± 3.5	40.8 ± 2.9	16.4 ± 0.5	58.9 ± 3
	B	85.7 ± 3.7	97.6 ± 0.9	77.7 ± 0.3	98.4 ± 1.8	76.0 ± 2
Trichophyton gypseum	A	53.4 ± 14.2	90.8 ± 2.8	57.4 ± 3.7	87.6 ± 2.2	52.5 ± 3
	B	84.4 ± 5.8	97.2 ± 1.6	90.6 ± 4.3	93.2 ± 2.3	91.4 ± 3
Trichophyton purpureum	A	61.3 ± 4.2	94.2 ± 3.3	24.9 ± 4.1	36.7 ± 6.1	6.5 ± 4
	B	72.2 ± 8.3	100.6 ± 0.0	38.3 ± 6.1	72.8 ± 3.0	36.9 ± 3
Trichophyton sulfureum	A	69.8 ± 6.3	95.0 ± 2.7	39.8 ± 2.3	78.0 ± 1.7	43.2 ± 1
	B	98.9 ± 6.3	96.2 ± 2.1	80.6 ± 4.3	87.0 ± 1.3	78.8 ± 2
Trichophyton crateriforme	A	87.5 ± 2.5	90.8 ± 2.8	27.1 ± 2.2	81.1 ± 1.4	30.9 ± 0
	B	93.7 ± 0.7	98.8 ± 1.6	79.5 ± 3.1	92.6 ± 3.1	79.2 ± 0
Achorion schoenleini	A	42.9 ± 3.6	73.7 ± 5.0	22.8 ± 5.2	74.1 ± 7.0	31.9 ± 0
	B	63.1 ± 4.6	91.8 ± 2.5	39.5 ± 3.9	82.1 ± 4.2	77.9 ± 4
Epidermophyton inguinale	A	47.0 ± 2.2	96.3 ± 4.7	53.2 ± 5.1	69.0 ± 6.5	32.9 ± 6
	B	70.6 ± 2.3	98.0 ± 2.8	78.2 ± 8.0	81.2 ± 4.1	81.1 ± 2
Monilia albicans	A	91.5 ± 1.5	77.6 ± 5.1	88.2 ± 5.4	96.6 ± 3.3	100.0 ± 3
	B	102.1 ± 2.0	91.7 ± 4.6	98.1 ± 5.6	101.8 ± 1.8	101.1 ± 5
Torula histolytica	A	93.0 ± 0.7	83.8 ± 3.1	102.3 ± 8.1	....	99.8 ± 2
	B	97.2 ± 3.9	92.4 ± 1.5	102.8 ± 2.7	....	100.6 ± 2
Histoplasma capsulatum	A	43.4 ± 3.0	80.0 ± 3.5	0	0	0
	B	71.1 ± 8.2	90.5 ± 1.9	41.5 ± 5.5	14.4 ± 2.5	4.1 ± 5
Sporotrichum schenkii	A	79.7 ± 3.3	93.4 ± 0.4	52.7 ± 3.3	74.9 ± 2.3	37.9 ± 5
	B	92.5 ± 5.7	96.6 ± 1.0	78.7 ± 1.4	84.4 ± 3.1	63.4 ± 6
Actinomyces transylvanensis	A	80.7 ± 2.3	93.3 ± 1.5	52.7 ± 3.3	74.9 ± 2.3	93.2 ± 1
	B	89.7 ± 2.2	108.5 ± 5.6	78.7 ± 1.4	84.4 ± 3.1	100.3 ± 2

* The figures represent percentages of growth in experimental plates compared with growth in control plates, for each fung "0" signifies no growth. Concentration A corresponds to 0.74 millimol per liter, and concentration B corresponds to 0.074 millim per liter.

more successful in young animals than in older ones, and among the older ones only the male rat is susceptible to the infection. Furthermore, in experimental blastomycosis (mice, rats, guinea pigs, dogs) the gonads are rarely affected. How far the prevalence of actinomy-

4. Emmons, C. W.; Olson, A. J., and Eldridge, W. W.: Studies on the Role of Fungi in Pulmonary Disease, Pub. Health Rep. **60**:1383, 1945.

5. Prior, J. A.: Geographic Distribution of Histoplasmin and Tuberculin Reactors Among Ohio State University Freshmen and Student Nurses Training in Columbus, Ohio, Hospitals, Pub. Health Rep. **62**:1608, 1947.

cosis among male human beings in contrast to the infrequency among females, can be evaluated may be debatable, but since the disease is not due to extraneous infection, but may develop wherever actinomyces are found in a saprophytic form, an estrogenic protective mechanism is well conceivable.

I have shown[6] that methyltestosterone and alpha estradiol exert a fungistatic effect in vitro on the growth of Trichophyton purpureum and Trichophyton gypseum. In the present study evidence is brought

*Pathogenic Fungi**

Progesterone	Pregnandiol	Diethylstilbestrol	Testosterone	Testosterone Propionate	Methyl Testosterone	Ethynil Testosterone	Desoxycorticosterone Acetate
37.1 ± 4.2	90.2 ± 2.3	0	29.0 ± 3.3	49.9 ± 3.7	9.6 ± 6.7	89.3 ± 2.1	52.9 ± 4.8
68.0 ± 3.8	96.8 ± 1.5	3.3 ± 4.4	79.7 ± 1.5	79.5 ± 7.5	88.9 ± 3.5	97.1 ± 0.9	72.1 ± 5.1
64.0 ± 3.8	89.7 ± 2.1	2.9 ± 3.6	55.0 ± 3.3	60.0 ± 2.9	45.0 ± 6.9	95.0 ± 1.3	83.6 ± 1.2
92.2 ± 1.9	97.4 ± 3.6	1.3 ± 2.3	70.6 ± 2.4	66.6 ± 1.6	87.5 ± 2.7	100.7 ± 4.5	95.9 ± 1.1
58.9 ± 3.1	85.6 ± 2.8	2.2 ± 1.1	43.7 ± 4.3	74.6 ± 2.5	40.3 ± 4.2	92.9 ± 2.5	78.8 ± 0.8
76.0 ± 2.8	90.1 ± 3.6	5.2 ± 1.1	75.1 ± 1.2	80.9 ± 0.5	92.6 ± 1.9	98.0 ± 3.3	91.9 ± 1.6
52.5 ± 3.5	100.6 ± 1.0	3.6 ± 2.4	52.8 ± 4.9	77.4 ± 0.5	57.7 ± 17.1	93.8 ± 2.8	84.6 ± 4.7
91.4 ± 3.8	99.6 ± 1.7	20.8 ± 6.1	90.0 ± 2.0	96.7 ± 2.2	94.4 ± 5.1	102.5 ± 4.0	93.6 ± 1.9
6.5 ± 4.9	78.7 ± 1.18	1.1 ± 1.8	6.3 ± 1.4	45.5 ± 10.5	5.4 ± 7.2	95.8 ± 4.2	64.0 ± 4.0
36.9 ± 3.5	98.8 ± 4.1	7.2 ± 5.4	63.3 ± 1.7	74.4 ± 5.7	83.7 ± 2.6	97.4 ± 4.1	77.5 ± 4.7
43.2 ± 1.3	97.9 ± 1.4	1.6 ± 8.9	25.2 ± 11.1	73.1 ± 4.1	17.3 ± 0.9	61.8 ± 4.0	86.5 ± 1.0
78.8 ± 2.5	101.6 ± 1.8	8.9 ± 7.9	83.1 ± 1.7	96.0 ± 5.3	90.7 ± 0.8	95.7 ± 3.9	93.5 ± 2.4
30.9 ± 0.8	94.1 ± 0.9	0.9 ± 1.5	39.0 ± 1.7	67.7 ± 2.9	58.3 ± 2.1	97.1 ± 1.7	71.7 ± 1.7
79.2 ± 0.4	98.5 ± 1.0	3.8 ± 4.2	74.1 ± 2.1	81.8 ± 2.5	94.6 ± 2.3	100.2 ± 0.3	92.9 ± 1.0
31.9 ± 0.7	93.8 ± 3.2	2.7 ± 3.6	46.3 ± 4.4	51.0 ± 3.3	0	89.4 ± 3.8	61.5 ± 2.2
77.9 ± 4.9	101.7 ± 1.4	9.3 ± 7.4	73.7 ± 5.6	70.3 ± 4.9	74.3 ± 2.5	97.8 ± 2.8	74.8 ± 5.4
32.9 ± 6.3	87.6 ± 1.1	0	53.6 ± 2.4	79.3 ± 2.1	18.2 ± 16.1	86.8 ± 2.5	67.2 ± 3.1
81.1 ± 2.8	92.9 ± 0.3	1.5 ± 2.6	84.1 ± 0.7	95.5 ± 0.7	77.3 ± 2.1	91.7 ± 3.3	83.8 ± 2.2
100.0 ± 3.7	102.0 ± 7.2	55.2 ± 4.6	88.7 ± 0.3	91.9 ± 1.4	77.6 ± 3.4	96.6 ± 2.3	96.5 ± 7.0
101.1 ± 5.8	108.7 ± 6.1	83.1 ± 3.1	97.2 ± 1.9	103.3 ± 4.3	89.2 ± 4.6	102.9 ± 1.0	102.6 ± 7.2
99.8 ± 2.1	91.0 ± 0.0	74.7 ± 3.9	76.9 ± 3.0	78.2 ± 4.6	71.7 ± 1.8	88.9 ± 3.3	91.2 ± 5.9
100.6 ± 2.7	96.5 ± 0.0	89.4 ± 5.0	92.9 ± 14.6	96.4 ± 2.9	82.1 ± 4.2	96.0 ± 2.7	99.3 ± 4.7
0	....	0	0	37.8 ± 8.1	0	89.4 ± 2.0	25.8 ± 2.8
4.1 ± 5.5	....	6.5 ± 6.5	48.4 ± 8.7	71.4 ± 3.9	0	100.1 ± 1.9	53.1 ± 4.1
37.9 ± 5.1	94.6 ± 1.3	10.6 ± 3.1	49.9 ± 3.1	70.9 ± 6.1	91.6 ± 2.6	57.2 ± 4.8	77.9 ± 0.3
63.4 ± 6.8	96.5 ± 8.1	31.5 ± 4.0	70.9 ± 4.0	88.4 ± 3.9	100.7 ± 0.5	73.2 ± 8.9	89.8 ± 3.9
93.2 ± 1.9	94.6 ± 1.3	0	52.2 ± 4.1	45.6 ± 4.5	29.5 ± 12.2	91.4 ± 7.8	70.1 ± 5.1
100.3 ± 2.9	96.5 ± 8.1	0	85.1 ± 4.5	64.6 ± 6.9	74.6 ± 8.9	99.8 ± 5.1	91.8 ± 4.0

forward on growth-inhibiting and genestatic effects of steroid hormones on fourteen pathogenic fungi.

MATERIAL AND METHOD

Estrone, alpha estradiol, estradiol benzoate, ethynil estradiol, diethylstilbestrol, testosterone, testosterone propionate, methyltestosterone, progesterone, ethyniltestosterone, pregnandiol and desoxycorticosterone acetate were dissolved in acetone and added to 20 cc. of melted 4 per cent dextrose agar, autoclaved and poured into Petri dishes. The molar concentration of the substances in the agar was 0.74 and 0.074 millimol per liter respectively. In the experimental part the 0.74 millimol per liter is noted as concentration A, and the 0.074 millimol per liter as concentration B. Saline suspensions were prepared of the following fungi grown on 4 per cent

6. Reiss, F.: Effect of Hormones on Growth of Tr. Purpureum and Tr. Gypseum, J. Invest. Dermat. **8**:25, 1947.

dextrose agar at room temperature: Microsporon audouini, Microsporon lanosum, Microsporon fulvum, Tr. gypseum, Tr. purpureum, Trichophyton sulfureum, Trichophyton crateriforme, Achorion schoenleini, Epidermophyton inguinale, Monilia albicans, Torula histolytica, Histoplasma capsulatum, Sporotrichum schenki and Actinomyces transylvanensis. With the exception of H. capsulatum, which was contributed by the American Type Collection, and Act. transylvanensis, which originated from the Lister Institute Type Collection, London, England, all fungi were recently isolated.

From each fungus a heavy suspension in saline solution was prepared and 0.1 cc. was inoculated in the center of each Petri dish. The growth of each culture was determined by the diameter of the growth after three weeks, at room temperature. As a control each fungus was grown on 4 per cent dextrose agar and the diameter measured; this was considered 100 per cent growth. The fungistatic effect was expressed in lowered percentage in case of inhibition, and where enhanced growth was observed figures exceed 100 per cent; "0" signifies no growth. Each experiment was repeated four times, and the average deviation is expressed in plus or minus (±) values (table)

COMMENT AND RESULTS

Fungistatic Effect.—On M. audouini, among estrogenic hormones (concentration A) only diethylstilbestrol and ethynil estradiol exerted an appreciable fungistasis; progesterone appeared to be less effective. While ethynil estradiol and progesterone elicit a proportionate increase in concentration B, in diethylstilbestrol the increase was 3.3 per cent from "0." Some of the androgenic hormones in concentration A also exerted a fungistatic effect, such as is elicited by the inhibition of methyltestosterone in concentration A (9.6 per cent), but an increase of growth up to 88.9 per cent is observed in concentration B, which does not appear proportionate with the ratio of the increased concentration. Similar is the increase from 29 per cent in concentration A of testosterone to 79 per cent in concentration B. Desoxycorticosterone acetate has an insignificant effect.

M. lanosum is inhibited by both alpha estradiol (8.6 per cent) in concentration A and by diethylstilbestrol (2.9 per cent) in the same concentration, whereas androgenic hormones show a rather insignificant effect.

M. fulvum is little influenced by estrogenic hormones, except diethylstilbestrol, which permitted only a 2.2 per cent growth in concentration A, and estrone, which permitted a 16 per cent growth in similar concentration. Androgenic hormones do not influence the growth to any great extent.

T. gypseum is appreciably inhibited by diethylstilbestrol (3.6 per cent) in concentration A, whereas testosterone (52.8 per cent) and progesterone (52.5 per cent), both in concentration A, disclose an almost identical inhibitory effect. Pregnandiol and ethyniltestosterone appear to enhance the growth, even in concentration B.

T. purpureum shows inhibition of growth by concentration A of diethylstilbestrol (1.1 per cent), methyltestosterone (5.4 per cent), testosterone (6.3 per cent) and progesterone (6.5 per cent). It is noteworthy that the proprionic ester of testosterone reveals a more vigorous growth (45.5 per cent) than testosterone (6.3 per cent) or methyltestosterone (5.4 per cent). Neither ethyniltestosterone (95.8 per cent) nor estradiol benzoate (94.2 per cent) have any appreciable effect.

T. sulfureum is inhibited greatly by diethylstilbestrol (1.6 per cent) and to a lesser degree by methyltestosterone (17.3 per cent), testosterone (25.2 per cent) and ethynilestradiol (39.8 per cent). No fungistatic experiments were made with concentration B of diethylstilbestrol, testosterone, testosterone propionate, methyltestosterone, ethyniltestosterone or desoxycorticosterone acetate.

T. crateriforme is appreciably inhibited by diethylstilbestrol (0.9 per cent), ethynil estradiol (27.1 per cent) and progesterone (30.9 per cent), whereas androgenic and the rest of the estrogenic hormones show little effect.

A. schoenleini is appreciably inhibited in concentration A of diethylstilbestrol, and no growth occurred in concentration A of methyltestosterone-containing mediums, whereas 74.3 per cent occurred in the concentration B. Ethynil estradiol shows some inhibitory effect (22.8 per cent) and pregnandiol in concentration B shows an enhanced growth (101.7 per cent) in comparison with the control.

E. inguinale is completely inhibited by diethylstilbestrol and appreciably impeded by concentration A of methyltestosterone (18.2 per cent).

M. albicans is not inhibited at all in its growth either by estrogenic or androgenic hormones, except by diethylstilbestrol in concentration A. In seven of these hormones an enhanced growth is noticed in concentration B.

T. histolytica is practically not inhibited by any of the steroid hormones. Ethynil estradiol and progesterone is favorable in concentration B.

H. capsulatum is completely inhibited in concentration A of the following hormones: ethynil estradiol, estrone, progesterone, diethylstilbestrol, testosterone and methyltestosterone. It is remarkable that concentration B of methyltestosterone also inhibits the growth of this fungus completely. This is the only fungus in the series investigated on which desoxycorticosterone acetate has a noticeably (25.8 per cent growth) inhibitory effect. Pregnandiol was omitted in this series.

S. schenkii is not inhibited appreciably by steroid hormones, except by progesterone (37.9 per cent growth). It is noteworthy that sporotrichon shows an enhanced growth (106.3 per cent) in concentration A of diethylstilbestrol.

A. transylvanensis is completely inhibited by diethylstilbestrol in concentration A and concentration B, and an appreciable reduction of growth occurs in methyltestosterone proprionate (concentration A).

GENESTATIC EFFECT

Besides the growth inhibition, investigation was directed also to what extent sporulation was inhibited with or without exerting a fungistatic effect.

Microsporon Audouini.—In contrast to the numerous pectinate bodies seen in the control, very few are observed in methyltestosterone-containing culture mediums.

Microsporon Lanosum.—In the testosterone-containing mediums (concentration A) an appreciable reduction of macroconidia was observed: this is reduced to almost nil in the diethylstilbestrol-containing mediums. The macroscopic aspect of the colony is also changed from a uniform feathery-woolly mass to a heaped up central knob, with complete loss of the greenish pigment. Similarly a reduction of macroconidia was observed in the estrone-containing mediums.

Microsporon Fulvum.—Nothing remarkable was noted with respect to M. fulvum, except that in the diethylstilbestrol-containing mediums (concentration A) the wall of the spores is thicker and they are of various shapes. In the ethynil estradiol-containing mediums (concentration A) there are hardly any macroconidia.

Trichophyton Gypseum.—Specimens from the testosterone-containing mediums (concentration A) disclose numerous macroconidia, whereas the paucity of macroconidia was recorded in the mediums containing alpha estradiol and ethynil estradiol (concentration A).

Trichophyton Purpureum.—Diethylstilbestrol-containing mediums (concentration A) reduce macroconidia appreciably, similar to testosterone.

Trichophyton Sulfureum.—There is a reduction of macroconidia in the mediums containing testosterone and diethylstilbestrol (concentration A), whereas in the methyltestosterone-containing mediums (concentration A) many large chlamydospores and an increase of macroconidia, which are pyriform in shape, are seen.

Trichophyton Crateriforme.—A genestatic effect is observed only in alpha estradiol-containing mediums (concentration A), where only chlamydospores and the absence of macroconidia is observed.

Achorion Schoenleini.—A. schoenleini are recorded only in the concentration B of methyltestosterone-containing mediums in the form of a mycelium composed of unusually fine hyphae. Chlamydospores are sparse.

Epidermophyton Inguinale.—Genestatic effects are observed in the testosterone proprionate mediums (concentration A), in the appearance of rudimentary fuseaux, but there is an almost complete absence of fuseaux in the mediums containing alpha estradiol, ethynil estradiol (20 mg. per hundred cubic centimeters) and pregnandiol (concentration A). There are, however, a large number of macroconidia visible in all the aforementioned mediums.

Monilia Albicans.—With respect to M. albicans, genestatic effects were not observed.

Torula Histolytica.—Genestatic effects were not observed with T. histolytica.

Histoplasma Capsulatum.—Genestatic effects of H. capsulatum in the form of a reduced number of macroconidia were observed in the concentration A of mediums containing diethylstilbestrol, alpha estradiol and estradiol benzoate.

Sporotrichum Schenkii.—No noteworthy genestatic effect was noted with S. schenki.

Actinomyces Transylvanensis.—No noteworthy genestatic effect was observed.

COMMENT

While the biologic effects of the investigated steroid hormones can easily be distinguished by their physiologic and pathologic effects in the human and animal body, their influence on the metabolism of pathogenic fungi does not reveal the same parallelism. Not only did various compounds influence the fungi in a different way, but the same compound also affected various species differently. Thus alpha estradiol plays an insignificant role as a fungistatic agent; moreover, it appears that M. albicans metabolized this hormone to its advantage. Estradiol benzoate enhances in a similar way the growth of T. purpureum, and not M. albicans. Ethynil estradiol exerts a complete inhibition on the growth of H. capsulatum and exerts partial inhibition on the rest of the fungi, except Torula organisms, which show enhanced growth. Estrone plays a less significant role with the exception of completely inhibiting the growth of H. capsulatum and partially that of T. purpureum. Progesterone produces complete inhibition of H. capsulatum, and permits only scanty growth of T. purpureum; whereas on the rest of the investigated fungi the results appear to be of little significance. Pregnandiol has no influence on the growth of the investigated fungi, except that the growth of M. albicans is enhanced. Diethylstilbestrol exerts a complete fungistasis on A. transylvanensis, E. inguinale, H. capsulatum and M. audouini and exerts an appreciable inhibition of growth on all the fungi, except S. schenki, the growth of which it enhances. Testosterone com-

pletely inhibits the growth of H. capsulatum and shows an appreciable reduction of the growth of T. purpureum and T. sulphureum. Testosterone propionate exerts little influence, except on H. capsulatum, which is slightly stunted. Methyltestosterone propionate completely inhibits the growth of A. schoenleini and H. capsulatum, and there is appreciable inhibition on T. purpureum, M. audouini and E. inguinale. Ethynil testosterone and desoxycorticosterone acetate have no significant inhibitor effect on the growth of the group of fungi investigated.

From a biologic point of view, as already mentioned, the fungistatic effect apparently does not depend on the specific estrogenic or androgenic character of the investigated compounds, but probably depends largely on their molecular structure. This would show that diethylstilbestrol is most effective on account of the double phenol ring, whereas compounds of the ketonic or hydroxyl group are less active as antifungal agents. Alpha estradiol and estradiol benzoate have a comparatively lesser antifungal effect; progesterone and pregnandiol reveal an almost similar effect. It is noteworthy that in a group of yeastlike fungi (M. albicans, T. histolytica) steroid (estrogenic as well as androgenic) compounds appear to be beneficial to their growth. Since it has been demonstrated by Peck [7] that in the extracted lipids of M. albicans and Blastomyces dermatitides, sterol esters and sterols are some of the constituents, it is well conceivable that the steroid compounds play a major role in the physiologic changes of that group. That these hormones are lacknig their characteristic biologic activity is demonstrated by the fact that neither the androgenic nor the estrogenic compounds act in a uniform way. There seems to also be an appreciable quantitative difference in the growth-promoting and growth-inhibiting effect of the individual estrogenic and androgenic hormones respectively. Desoxycorticosterone acetate resembles in its effect partly the estrogenic and partly the androgenic hormones.

From these rather diverse observations no final conclusion can be drawn as to what effect steroid hormones have on the infection in the human or animal host; but one cannot deny the possibility that steroid hormones may affect the course of a mycotic infection directly, as observed in microsporon infections of the scalp, or through their well known effect on protein anabolism, may alter the structure of the protein molecule in such a way as to make the growth unsuitable for a certain group of pathogenic fungi. This may be particularly true in relation to H. capsulatum, which is inhibited by six steroid hormones. The genestatic effect of some of the steroid hormones also indicates that not only is there a reduction of growth but also a reduction of conidial structures, which could be interpreted as evidence not only of growth

7. Peck, R. L.: The Lipids of Fungi with Special Reference to Pathogenic Fungi, Ann. Crypt. & Physiopath. **6**:167, 1947.

stunting but also of reduction of virulence. This is particularly obvious in the reduction of macroconidia of M. lanosum and M. fulvum in mediums containing the diethylstilbestrol and estrone. Similar is the effect of estrogenic hormones on M. audouini, T. gypseum, T. purpureum, T. sulfureum, T. crateriforme, E. inguinale and H. capsulatum, whereas the audrogenic-genestatic effect is negligible, as for example in M. audouini, M. lanosum, T. sulfureum, A. schoenleini and E. inguinale.

SUMMARY AND CONCLUSION

Twelve hormones have been investigated in relation to their fungistatic and genestatic effect on fourteen pathogenic fungi. No parallelism can be drawn between a specific physiologic effect and the fungistatic effect. Estrogenic hormones exert a more appreciable genestatic action than androgenic hormones. The most effective fungistatic compound is diethylstilbestrol, whereas the rest of the investigated steroid hormones show a variable fungistatic effect, which depends most probably on their molecular structure. Monilia albicans and Tortula histolytica show an enhanced growth in steroid hormone-containing mediums.

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PRACTICAL MEDICAL MYCOLOGY

The Culture of Fungi as an Office Procedure

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LOS ANGELES

MEDICAL mycology has failed to interest more than a few practitioners, even those whose specialties include mycotic diseases. We believe the fault lies in the complicated nature of the methods, which can be simplified so that every physician may become proficient in dealing with the fungi encountered in his field.

In recent years, simplification of many phases of medical mycology has been carried out to an admirable degree. The first laudable attempt in book form was that of Jacobson [1] in 1932. The texts by Lewis and Hopper,[2] in 1939; Schwartz,[3] in 1943; Conant, Martin, Smith, Baker and Callaway,[4] in 1944, and the revision of Henrici's text by Skinner, Emmons and Tsuchyia,[5] in 1947, have created a new wave of popularity for this subject. Other workers in this field have also made valuable contributions.

The usual methods of culture in mycology remain so antiquated, inconvenient, time-and-space–consuming, dirty, and at times malodorous, as to constitute an undesirable chore for the average busy physician in his office. No matter how well trained in mycology a practitioner

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1. Jacobson, H. P.: Fungous Diseases: A Clinico-Pathological Text, Springfield, Ill., Charles C Thomas, Publisher, 1932.

2. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 1, Chicago, The Year Book Publishers, Inc., 1939; ed. 2, 1944.

3. Schwartz, J. H.: Elements of Medical Mycology, New York, Grune & Stratton, Inc., 1943.

4. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944.

5. Skinner, C. E.; Emmons, C. W., and Tsuchyia, H. M.: Henrici's Molds, Yeasts and Actinomyces, New York, John Wiley & Sons, 1947.

may be, he cannot use that knowledge efficiently unless cultures are inoculated in all doubtful cases. Many of the objectionable features usually encountered may be eliminated by the method outlined in this study. It is particularly well suited to the needs of the practitioner in his office and is of equal value in large institutions.

When culture of fungi or bacteria on artificial mediums is indicated, it is customary to use glass containers of two types: the ordinary culture or test tube and the Petri dish; several sizes of each are available and in common use. Many other types—glass tubes, vials, bottles and jars of various shapes and sizes—have been sporadically used as they have appeared on the commercial market; none has achieved general popularity. A review of the literature does not reveal any exhaustive study of modern glass containers to find the one most suitable. The purpose of this report is to present in detail the results of such an investigation and to record the impressions gained during the past four years from use of the container finally selected in the offices of many private practitioners and in several large institutions. No claim is made to priority in the use of any of the features exhibited by this container, or to any combination of them other than that furnished by it.

The usual culture tube has many disadvantages. It is easily broken by being dropped or by being struck against hard objects. Its closed end is hemispherical, necessitating a rack for its support; and where numbers of tubes are used, much more than the minimum space is needed. Its cylindric shape allows it to roll when laid flat, unless on an absolutely level surface. It is almost impossible to write on a label previously placed on such a tube, and labels are difficult to read whether longitudinally or circularly placed. It is usually necessary to turn the tube in its rack to bring the label into view, and many tubes must be so turned when one is searching for a specific culture among many. When agar slants are prepared in tubes of average size, the surface available for culture growth is long and narrow, approximating only 3 or 4 sq. cm. The agar solidifies into a hemicylinder, which exerts the distorting effects of a planoconvex lens when the culture is viewed from below, and the central portion is so thick that even mild caramelization of the medium or inclusion of blood, dyes or other colored substances in its formula causes an undesirable degree of opacity. A less noticeable distortion is produced by the cylindric glass surface when the culture is viewed from above. The average tube is at least twice as long as necessary, and implantation or removal of small portions of the culture growth for replantation, isolation or study by wet mount is difficult because of the lack of leverage and control resulting from the distance of the operator's fingers from the point of attack. The best instrument for such operations is a platinum wire flattened into a sharp-edged

spade at the tip and held in a handle. If this wire is long enough so that the handle does not also enter the tube (and hence require sterilization with a flame), it is not rigid enough to allow portions of tough colonies to be cut out and removed; if the handle must also be heated, much time is wasted in cooling. When the tip of the wire is inserted into the tube, the operator's hands are so far apart as to make the procedure difficult to accomplish without contamination, the fragment destined to be inoculated being frequently dislodged by vibration or jolting.

The method of closing the tube with a cotton pledget has several disadvantages. Tubes cannot be prepared in large quantities at one time because the medium soon deteriorates by drying. Preservation of desirable cultures for future reference can be accomplished only by hermetically sealing with paraffin or wax. This seal is easily broken and requires such careful handling that a large permanent collection can be assembled and maintained only with great difficulty. When it is desired to carry cultures in the pocket, the cotton pledget is frequently dislodged and lost, and widespread contamination may occur, always undesirable and even dangerous in the case of some species. When material is being planted or transferred from such tubes, the cotton pledget, which must reenter the tube, cannot be sterilized by the flame without one's frequently burning the fingers. Gaseous products arising from the growing fungus colony diffuse through the cotton plug and permeate the laboratory. Tubes have the advantage that they are more easily cleaned than containers of any other shape, and their original cost is low. No other advantages are apparent.

The Petri dish also has disadvantages. It cannot be hermetically sealed. It is fragile and expensive, and its shape precludes compact storage in numbers. If stored in stacks, many dishes must first be lifted to obtain the desired culture. If the dishes are labeled on the edge (the only place where labels remain visible when the dishes are stacked), it is usually necessary to turn them to bring the labels into view. If they are labeled on either face, visibility is obscured; the labels are soiled by the other dishes when stacked, and many dishes must be handled to select a desired culture. It is difficult to transport specimens in such containers without breakage and resultant contamination.

The Petri dish, however, is superior to any other container for the separation of mixtures of organisms; the giant cultures, which its use affords, are excellent when new species are to be studied and photographed. Experienced workers will feel handicapped unless the Petri dish is available when identification of a culture is difficult.

Over three hundred varieties of small glass containers, of all shapes, sizes and colors, displayed in catalogues and showrooms of major firms in the containers' industry, as well as containers observed on shelves

of pharmacists, chemists and cosmeticians, and even those containing pharmaceutic samples, were considered in this study. Every attempt was made to cover the commercial field.

A considerable variety of small bottles are produced in such vast quantities by mass production that the cost per unit is extremely low. Several varieties of such containers can be purchased, new and clean, for approximately two thirds of the labor cost alone involved in cleaning an equal number of ordinary culture tubes. Included in such cost is that of closure, whether it is cork, screw cap or pledget. It was felt that if a suitable container could be selected from this group, the principal advantage afforded by the use of tubes—that of easy cleaning—would be nullified. Cultures no longer desired could simply be thrown away. This advantage is of more benefit to the physician in his office than to institutions, where cleaning of apparatus is done in a well organized department. However, the same cost relationship was found to exist in such institutions.

Preliminary trial of several varieties of containers within this price range was made in order to select those with the least disadvantages. For routine culture, bottles duplicating the large surface afforded by the Petri dish were found to be unnecessarily bulky. An agar surface approximately 4 cm. square (16 sq. cm.) was found to be adequate in all but a few instances, in which transfer to a larger surface was then carried out. A few containers were available which afforded this area and which, in addition, presented flat surfaces similar to those of the Petri dish. Two containers also had flat or only slightly curved surfaces at the narrower edges, and both were flat bottomed and equipped with plastic screw caps. Both were approximately 4 cm. square and 1.6 cm. thick. The production of one of these containers is controlled by a large pharmaceutic company, and it is not easily obtained in small quantities; the other is readily available and has become our final selection[6] (fig. 1).

These bottles are manufactured by being blown into molds, and all corners are so heavily reenforced by an extra thickness of glass that they are highly resistant to breakage: they do not break when accidentally dropped from table height or by being intentionally thrown several feet across the room against surfaces other than metal or concrete; several may be carried safely in the same pocket.

The plastic-threaded cap closure furnishes an immediate hermetic seal whenever desired; bottles may be prepared for culture in any desired quantity and immediately closed tightly; this type of closure

6. Bottles of this type are easily obtained in almost every large city in the United States through the retail outlet branches of the Owens-Illinois Glass Company, of Toledo, Ohio. This item, a ½ ounce (15 cc.) perfume bottle with black plastic screw cap, may be identified by the number A-4350.

prevents any deterioration of the medium through drying, and can thereby be kept until needed. The only surface of the screw cap which can collect and transfer spores of air-borne contaminants is the circular fiber disk which is set in the bottom of its cavity. If the cap is held with the opening directed downward during the planting of the culture, the chance of air-borne contamination is so small that it is safe to dispense with the sterilization of the cap.

Bottles are prepared in large quantities by filling them approximately one-third full with melted medium (about 5 cc.). The caps are screwed on loosely, so that gaseous transfer into and out of the bottle may

Fig. 1.—Exact size of bottle recommended for culture of fungi.

take place during sterilization by heat. They are then stacked in baskets, autoclaved for twenty minutes at a pressure of 15 pounds (6.8 Kg.), removed and immediately placed so that one of the flat faces of each bottle is slanted approximately 10 degrees from the horizontal, with the cap on the higher level. The correct degree of slanting is that which permits no agar even partially to obstruct the neck of the bottle or to touch the upper face of the bottle near its bottom, and thus lessen the surface area of the medium. The bottles are allowed to cool thoroughly in this slanted position before the caps are tightened, in order to prevent the formation of a partial vacuum. If such a vacuum is present, opening the cap allows a sudden inrush of air, which may carry contaminating spores. The cap is sometimes removed only with difficulty if it is tightened before cooling, and the

paper and cardboard disks within the cap may be partially sucked into, or firmly adherent to, the mouth of the bottle.[7]

The technic of inoculation is simple. The bottle is held in the left hand, the inoculating instrument with the inoculum adherent to it, in the right. The cap of the bottle is grasped within the curve of the fifth finger of the right hand, and the bottle (not the cap) is turned until the threads are no longer engaged. The hands are separated just enough to allow entry of the instrument, which is easily and accurately accomplished (fig. 2). The opening of the bottle, as well as the inner surface of the cap, should be directed downward to minimize contamination through falling air-borne spores. The cap is then replaced, but not completely tightened, for reasons which will be explained later.

The opening afforded by these bottles is somewhat smaller than that of standard tubes, but it is not a disadvantage, for it greatly decreases the possibility of air-borne contamination. Moreover, the short planting

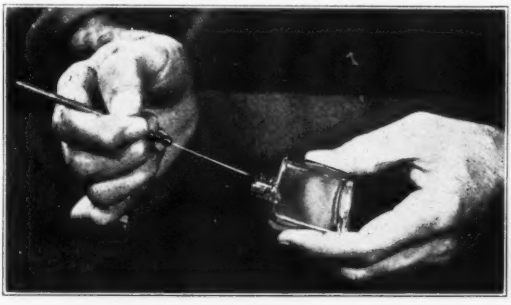

Fig. 2.—Technic of inoculation. Note accurate control afforded by the short planting wire and bottle.

wire and the short distance between the operator's fingers and the site of the operation increase accuracy and minimize the chances of contamination. It has been found possible to plant cultures with this technic, without sterilization of the opening of the bottle by flaming, in rooms other than those where cultures are opened frequently for examination or in rooms where there is excessive motion of the air. Cotton pledgets are unnecessary; their function is duplicated by allowing the screw cap to remain incompletely closed, by about a half-revolution. It is important to allow ingress of air needed for metabolism and for the escape of noxious gases, such as those remaining from the flaming of the bottle opening, from alcohol and antiseptics introduced with the specimen and from those produced by the fungus itself during growth.

7. Bottles properly prepared for culture may be obtained from the Derm Medical Company, 3053 Rosslyn Street, Los Angeles 41, at about $7 per hundred.

As soon as a colony has reached the desired size, however, the cap may be tightly sealed and no other odorous gases will escape. This practice reduces the musty smell or odors of fermentation usually present in mycology laboratories.

If it is desired to maintain viability of the organism, the cap may be loosened for a short time at intervals of a week or so. Considerable overgrowth and pleomorphism may be prevented by this procedure. When a culture colony has reached a stage at which it is a desirable specimen for teaching purposes, it may be preserved for several months by simply tightening the cap. This period of preservation may be extended into years by removing the cap and coating the threads within it with plastic or asphaltic cement. The growth of the colony will continue for a week or more, but will then gradually cease because of anoxia and accumulation of toxic products within the hermetically closed container. A few drops of solution of formaldehyde U. S. P. on a cotton pledget placed in the neck of the container, as recommended by Lewis and Hopper,[8] stops the growth process at once, but the delicate colors of many genera gradually fade because of the chemical action, and some genera, such as Trichoderma, Phoma and Pleospora, lose all semblance of their usual form.

The surface of the medium made available by these bottles allows colonies grown thereon to assume a disk shape, so that their gross characteristics can be more easily observed than when grown on test tubes. The thin layer of agar has such a degree of transparency that the subsurface growth of the colony may easily be observed from beneath. This is an advantage in identification of several important genera of fungi, notably Candida (Monilia). For the same reason color, which is produced by some species and frequently diffused into the medium, may be more easily seen. This ease of observation is useful, for example, in the identification of Trichophyton rubrum and Trichophyton rosaceum and Microsporum canis and Microsporum audouini.

Cultures no longer desired may be disposed of simply by throwing them into the wastebasket. Pathogenic species, however, should be killed before disposal by placing a few drops of solution of formaldehyde U. S. P. in the culture bottle and tightening the screw cap.

If cultures are to be transported in the pocket a short distance, contamination is prevented by the tightened cap. The resistance to breakage, together with the hermetic seal afforded by the screw cap, makes this bottle an ideal container for the transportation of specimens of fungi by mail. The thin layer of agar is so light in weight that it

8. Lewis, G. M., and Hopper, M. E.: Preservation of Fungus Colonies by Formaldehyde, Arch. Dermat. & Syph. **34**:686 (Oct.) 1936.

does not become dislodged easily and withstands a greater degree of jolting. Sufficient oxygen is usually entrapped to insure viability for a week or more.

The square corners of the bottles permit them to be alined with faces contiguous on shelves 6 mm. thick, 4 cm. wide and placed 7 cm. apart. Ten bottles so placed occupy only 11 cm. of shelf length. A wall surface of 1 square meter will accommodate 750 such cultures (fig. 3). Since fungi grow advantageously without light, a door may be hinged at one of the edges of the series of shelves to form a cabinet, which

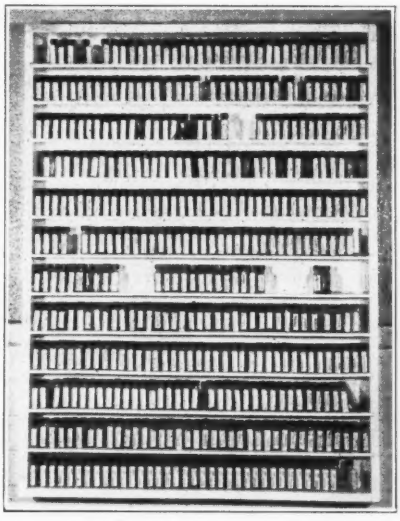

Fig. 3.—Set of shelves providing space for 450 cultures of fungi.

may be closed when not in use. Figure 4 shows the most elaborate cabinet we have as yet devised. Details of this and of other types of cabinets and shelves will be published at a later date.

The bottles are conveniently labeled on one of the narrow edges, which remains fully visible in the cabinet. Culture bottles may be prepared in quantity by affixing paper labels in advance of their use. These labels are also provided with written numerals, which will later serve to key each culture to the corresponding patient's chart. It is easy to write on such labels, and since some operators prefer to use an object approximately 4 cm. in height, such as a book or a block of wood, on which to rest the writing hand, the bottle can be held against the edge of this object with the label presenting upward. Immediately after the planting, the patient's name, the date and the site from which

the specimen was obtained are written on the label, and the key numeral previously placed thereon is transcribed to the patient's record.

If a small space on each shelf of the laboratory cabinet is left unoccupied, it is easy to examine all the cultures recently inoculated for

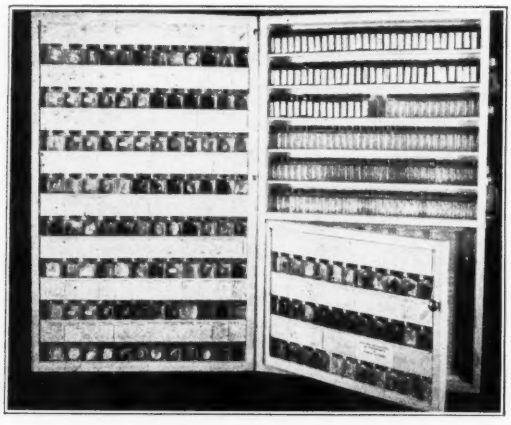

Fig. 4.—Hinged wall cabinet providing space for 120 permanently preserved samples of gross cultures, 180 actively growing cultures and 400 permanent preparations for microscopic study.

Fig. 5.—Recently inoculated cultures may be inspected for beginning growth by turning each bottle slightly to bring the face into view. By scanning the labels, any culture may be selected without touching others.

beginning growth without removing each bottle from the shelf. With the index finger, one simply moves each bottle in turn on a vertical axis, so that its face becomes visible (fig. 5). Any culture may be selected without touching any other bottles, by scanning the labels.

The sterile instruments used for obtaining the specimens from patients must be of a size and shape appropriate for planting the material directly on the surface of the medium. A convenient instrument for obtaining specimens from the surface of the skin is the small blade with a curved tip (no. 15) of the conventional removable blade scalpel. This instrument will also serve to transfer purulent material from sinus tracts or a granulomatous ulcer. Larger blades will not enter the small mouth of the bottle. If an epilating forceps, of a size small enough to enter the bottle opening, is chosen, it may also be used to plant epilated hairs directly onto the surface of the medium. When one is clipping fragments of nail for implantation, it is convenient to use the small curved forceps of the type commonly called mosquito forceps, to

Fig. 6.—No other equipment is needed for inoculating cultures directly from suspected lesions.

prevent the loss of the fragment by the sudden force imparted by the clipper. The forceps then provides an ideal instrument for direct implantation of the fragment onto the surface of the agar. To insure sterility, these instruments for implantation need only be kept in 70 per cent alcohol or in one of the sterilizing solutions in common use. This method of direct implantation is the simplest which can be devised and is much to be preferred to the placing of material in folded papers or other containers for later implantation, with or without intervening chemical treatment. The surface from which the specimen is to be obtained should always be cleaned thoroughly with 70 per cent alcohol; any significant pathogenic fungi which are present will still remain after such cleaning, and the chance of contamination from saprophytic fungi and bacteria is minimized.

It is simple and inexpensive to equip all rooms in which patients are usually examined with a set of instruments appropriate for direct inoculation, together with a supply of bottles prepared with sterile

medium, sealed against deterioration and provided with attached gummed labels bearing key numerals (fig. 6). Cultures may be inoculated whenever desired, sealed again and replaced, without a trip to the laboratory. A fraction of a minute suffices for the entire procedure. At the end of the day, all cultures may be collected and filed in numerical order in the laboratory cabinet.

SUMMARY AND CONCLUSIONS

After an extensive survey of all available containers, a glass bottle of specific size and shape has been selected which is believed to be an ideal vessel for the routine culture of fungi pathogenic to man.

A bottle of this type is superior to the usual test tubes in every category and should entirely replace them. It should also partially replace the Petri dish.

It is considerably cheaper to use these bottles once and discard them than to pay the labor cost of reconditioning an equal number of test tubes.

Requirements for laboratory space are kept at a minimum because of the superior facility of storage.

Use of this container renders it easy to keep the laboratory clean and up to date.

A method of inoculation is described which is so rapid and convenient that there should be little temptation to ignore the culture of fungi when indicated.

This method of culture should provide another step in the current popularization of medical mycology.

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ABSTRACTS OF DISCUSSION

DR. ROYAL M. MONTGOMERY, New York: The presenters' excellent paper and exhibit should stimulate every dermatologist to do more laboratory work in mycology. This type of investigation is overlooked in many offices. Every patient who has a dermatosis suggestive of a fungous infection should have a mycologic examination. The treatment of some types of eczema of the hand or foot would be more successful if one knew that the eruption was of fungous origin. In the majority of cases the mycotic infections are superficial, and a direct mount in potassium hydroxide and a culture on Sabouraud's medium should be made. Both procedures are simple. With a little study, every dermatologist should be able to identify a positive slide and to recognize the common fungi.

This compact bottle for culturing is a valuable addition to every dermatologist's laboratory. One cannot deny that this container has many advantages over the standard test tube and Petri dish. I have been using test tube slants of Sabouraud's medium for the past sixteen years as the standard office culture method. These I inoculate with material taken with a Bard-

Parker scalpel equipped with no. 15 blade and carried directly from the patient to the test tube. This method, as Dr. Wilson mentioned, is better than saving the scales or hairs in a sterile paper until later for inoculation or examination. However, it is sometimes more convenient for one to examine and plant the specimens after office hours. The labeling of test tubes is not difficult. It is important always to list on the label the name, date and location from which the specimen was taken. Subcultures from these slants can be taken without difficulty if a stiff instrument or standard scalpel with a no. 15 blade is used. I place these tubes, stoppered with a tight cotton plug which has been flamed, in the bottom drawer of a desk and examine them frequently. No tube is discarded until it is four weeks old so that no slow-growing organism will be overlooked. I have never noted any objectionable odor from the test tube cultures. It is a definite advantage of the test tube slants that multiple inoculations, usually three or four, can be made in each tube. These slants are easily obtained through the bacteriologic laboratories of most hospitals. In the average office, a dermatologist would rarely have more than fifty test tubes with active cultures, and these tubes would conveniently fit in a desk drawer, which obviously should be dark.

I believe that the bottles which are recommended are excellent for stock cultures. For dermatologists who must conserve space in the office or hospital laboratory, these bottles are advantageous. It will be difficult to convert men to the use of this bottle when they have been used to test tube slants and have had satisfactory results. However, I am going to give them a trial.

Dr. William L. Dobes, Atlanta, Ga.: Medical mycology, especially the related laboratory procedures, is a comparatively new specialty. Only in the past ten or fifteen years has this branch of medicine been emphasized as a routine in teaching young dermatologists. Those who have had practical training in mycology appreciate the value to diagnosis of comparing clinical impressions with laboratory procedures. Drs. Wilson and Plunkett have spent much effort in an attempt to simplify and make more attractive the laboratory procedures in mycology. Whether we fully or partially agree or disagree, similar papers should be encouraged in an attempt to improve and better a recent, but important, phase of dermatology.

The perfume bottle described by the authors has some apparent advantages over the test tube. The use of this type of container would appear to be of value in laboratories where large numbers of cultures are being taken each day and where the containers are often roughly handled by the technicians. As an aid in teaching, the wide surface of the bottle makes it easier for a student to observe the fungus growth through certain characteristic stages. Other advantages, as described by Dr. Wilson, may prove important to a laboratory or to students in a teaching institution, where there are much handling and transferring of cultures.

In my private practice I use culture tubes, with satisfactory results. The average dermatologist does not make his own culture tubes. It is more economical, time saving and convenient to have a private hospital or laboratory prepare them. The laboratory covers the plugged openings of the test tubes with wax paper, which is fastened with a rubber band. In this manner, I find my culture medium satisfactory even after six weeks, especially when it is kept in a cool place.

I have found contamination of my medium to be infrequent. Since only the platinum wire is forced into the culture medium, it is not necessary to heat

the handle. Wiping the handle off with an alcohol sponge is rapid and satisfactory. As soon as the culturing is done, a label with the date and name of the patient is pasted on the tube. All other data are permanently entered on the patient's chart. In dermatologic practice, the common pathogenic fungi are not numerous. Usually in one to two weeks the cultures are sufficiently typical. Once a diagnosis is made, the used culture tubes are discarded, or they are returned to the laboratory at the end of each fortnight and a supply of fresh medium is obtained. A trained mycologist usually does not need culture transplants for diagnosis. If the growth is atypical, the microscopic examination will usually clinch the diagnosis; it therefore is not necessary to keep cultures long enough for odors to develop. The label and slant are always placed face forward. When they are properly placed, the name and culture can both be quickly recognized without one's having to turn or manipulate the test tube. Cases in which the infection is resistant to treatment or in which the diagnosis is uncertain are the ones in which cultures are most frequently made. The average practitioner need not, nor cannot, afford the time to make cultures on every lesion clinically suspected of being caused by fungi. A questionnaire was mailed to fifty well known certified specialists in dermatology in various parts of the country, and forty-two responded. The question was, "How many mycologic cultures are taken each week in your private office?" Thirty-one made less than four cultures a week; only two made more than ten cultures a week.

I have found two bad features about the perfume bottle. In order to inoculate the center of the culture medium, a long platinum wire (about 1 inch) is needed. If a microscopic examination of the culture is desired before the culture reaches the end of the opening again, a long platinum wire is needed, and this makes it difficult to remove satisfactorily the desired part of the culture. If a label is placed on the front of the bottle, it may obstruct the view of the culture. When labeled on the side, the bottle must be turned on the shelves whenever a certain patient's culture is looked for, and vice versa. The platinum wire I use in the culture tubes is only ¼ inch (6 mm.) long, and is therefore, firm and practical for all purposes. A wire of this length will hardly reach past the neck of a perfume bottle.

The direct microscopic examination seems to be the more popular with dermatologists today. However, I agree with the presenters that the cultural methods should be stressed and popularized to a greater extent. It will lead to more correct diagnoses.

The authors' process of elimination in an attempt to find the most suitable container was no easy task and required time and patience. May I congratulate them on their excellent paper?

DR. T. BENEDEK, Chicago: I congratulate the authors on their execellent exhibit. I can appreciate the assiduous work and toil which they have carried on with such ingenuity for many years. The perfect didactic presentation of their method deserves the highest praise. The handy little culture flasks have some advantages for office use; they have also some disadvantages when compared with the old-fashioned agar slant in the culture tube. Proper collection of infected material and its inoculation constitute only one phase of the procedure. The most important part is the microscopic diagnosis of the culture. The direct microscopic examination of the culture in these flasks is of course impossible under the microscope. For this purpose the culture test tube still holds an uncontested first place. More than twenty years ago I constructed and published a description

of a special microscopic stage clamp and suggested a certain type of inoculation of the culture tubes. This method made it possible to culture the infected inoculum and to make its microscopic diagnosis under the microscope through the wall of the test tube without touching or destroying the fungus growth in its habitat. In the case of Microsporum gypseum, for instance, the microscopic diagnosis could be made in seventy-two hours; in that of M. canis, in seven days. I should like to mention the ingenious mycotheca, with the hidden storage space for hundreds of slides. I hope the authors will publish a sketch of this handy mycotheca and will permit its reproduction by others.

I want also to extol the flawless presentation of great numbers of common pathogens in the painstaking drawings from the hand of Dr. Wilson. This is a beautiful achievement. I hope that these drawings, with proper explanatory text, will soon be made available in book form for the benefit of all medical mycologists in command of the English language. Up to now we have had only one similar classic work in the entire mycologic literature, the publication by Pollacci and Nannizzi on the "Pathogenic Fungi of Men and the Animals," published at Siena in 1922 in Italian.

DR. JAMES HERBERT MITCHELL, Chicago: I congratulate the presenters on receiving a silver medal.

I hope Dr. Wilson did not spend too much time, six years or so, in getting the idea of the flat bottle. About 1921, I published a paper in which I suggested the use of the whisky flask (Further Studies on Ringworm of the Hands and Feet, ARCH. DERMAT. & SYPH. **5**: 174 [Feb.] 1921). That was in the days before the screw cap. I used cotton, and it was perfectly satisfactory. The paper that I speak of was read before this Section in 1916. I have never been able to decide whether I did more harm than good in presenting that paper, for, inasmuch as the paper called attention to ringworm of the hands and feet, the idea immediately became nation wide that everything on the hands and feet must, of necessity, be of fungous origin. Later I presented a paper before the American Dermatological Association in which I tried to undo the damage I did in reading that paper. Since then, I have been going all over this country, trying to point out that, as Dr. Wilson has said, we must make cultures and we must use the microscope. However, I find no difficulty in keeping cultures long enough with the ordinary tube. I use a 1 by 6 inch (2.5 by 15 cm.) tube, stoppered with cotton and then cover the stopper with tin-foil and a rubber band. This serves my purpose very well.

As for the use of the platinum wire, I see no reason why, if one uses an aluminum holder, 6 inches long, with a fairly stable wire, the handle cannot be flamed. That does away with all use of alcohol.

It is easy to make one's own medium. An ordinary pressure cooker is adequate. I make my own and like it.

DR. GEORGE H. CURTIS, Cleveland: I think the presenters' method of culture and preserving fungous cultures for mycologic study is an excellent one. I stumbled onto the efficacy of this method in 1945, when the pathologist in the Army station hospital ran out of culture tubes and we thought of using a flat bottle. At first we used a ½ ounce (15 cc.) ordinary dispensing medical bottle. Later we changed to a 1 ounce (30 cc.) size. I have had a number of cultures in these bottles for a little over three years, and the mediums and cultures are well preserved as to transparency and color. There has been no shrinkage due to drying out of the medium. Most graduate students in dermatology who are taking their basic training in the universities and hospitals attempt to obtain a collection of fungi for comparative studies in their practice. I once obtained a

set of the cultures. They were in large tubes with a cotton button and were sealed with paraffin. They quickly dried up and became useless. Tubes with cotton buttons, corks and paraffin seals also do not last long. I have tried sealing off the top of a culture tube, but most of them crack and break on handling and become useless.

The bottle method is excellent for preserving cultures. One may allow the culture to grow to proper size, add a few drops of solution of formaldehyde U. S. P. and screw the cap down tight. The culture and color may be preserved almost indefinitely.

Dr. Murray C. Zimmerman, Westwood, Calif.: I have used test tube slants, but for the last year and a half I have used these bottles; and I disagree with criticisms made of them by persons who have never used them. I think that every one here who has worked with test tubes has had the culture medium dry up to a useless condition, either before or after inoculation. In contrast, in the small bottles, my colleagues and I poured our first series of five hundred slants eighteen months ago. The unused bottles are still in perfect condition. Of the ones which were used, the cultures are in perfect condition. The surface area of the Saboraud medium in the bottle is large, as Dr. Wilson said, and the growth characteristics are the same as those in tubes or on Petri dishes.

I disagree with Dr. Benedek that one cannot use the small bottles under a microscope. I believe they can be seen better, for there is no lens effect from the curve of the test tube. They are particularly suitable for examination with the binocular dissecting microscope.

As has been suggested by previous commentators, it is true that one can cover the test tube first with cotton pledgets, then with waxed paper and then with a rubber band, or with tin-foil and a rubber band, but this does not completely eliminate evaporation. Practically, these materials may not be conveniently at hand, moreover, all these steps take time, particularly in an office where not much culture work is done. I would confirm the statement that it is indeed a "simple twist of the wrist" to use these small bottles.

I would also point out the considerable factor of danger in culture of a fungus such as Coccidioides immitis, which has repeatedly infected laboratory researchers. I have not been able to break any of these bottles, although they have been dropped off the desk and knocked around considerably. It is comforting to know that spores of C. immitis are not floating around the laboratory because some one dropped a plate or a tube of the culture. If these bottles drop on a cement floor, they bounce but do not break. In addition to their mechanical strength, the small neck opening reduces to a minimum both the contamination of the laboratory by spores from the culture and contamination of any culture by free-floating air-borne spores.

I agree that these bottl are the most convenient, least bulky, cheapest and safest culture containers available, and that they are particularly suited to the needs of clinical practice. Dr. Wilson and Dr. Plunkett do not lack experience with other methods mentioned, and I doubt whether their procedure will be condemned by any one who has tried it.

Dr. J. Walter Wilson, Los Angeles: It would be surprising if in fifteen minutes we could convince our colleagues of many years' experience in mycology that they should change their basic culture flask.

We do not think this procedure has its greatest appeal to those who are fully competent in mycology. However, most physicians do not employ any method of culturing fungi. If they are furnished with a simpler and easier method

with which to work, we believe it will result in suspected materials being planted more frequently and a complete mycologic study of more patients.

Dr. Montgomery said that he liked tubes because of several features. He neglected to mention one fact. We feel that it is not necessary to flame the openings of these little bottles because the opening is so small that air-borne contamination does not occur very frequently; so we save a trip to the laboratory to flame the bottle. Dr. Dobes said he kept his unused agar slants as long as six weeks before drying occurred. In our climate culture tubes dry more quickly. One may pour 1,000 of these bottles, if desired, and they will be good for two or three years. That should be more obvious to the physician who plants only a few cultures. If he uses them only once in a while, he is likely to find that when he needs a culture tube the only ones he has available are dry. As to the long wire, no longer wire is needed for this little bottle. The holder of the wire needs only to be small enough to enter the neck of the bottle. We do not label the bottles on the face; we label them on one edge, which is not needed for any other purpose. Neither the front nor the back of the bottle is obscured.

I wish to thank Dr. Benedek for his kind words concerning our series of identification drawings of fungi and to remind him that such art work itself is not difficult. In the present instance it was the intimate knowledge of these organisms possessed by a cryptogamic botanist, Dr. Plunkett, which made it possible.

I have been asked to state where these bottles may be obtained. They are available in any large community at very little expense.[7]

ROENTGEN RAY TREATMENT OF THE EYE

Further Experiences

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FIFTEEN years have passed since we first used roentgen rays for the treatment of diseases of the eye.[1] It would now seem advantageous to report on recent experiences with treatment, as well as to describe any late effects of such treatment on the cornea and lens of those eyes treated more than five years ago.

In a previous paper [1] we discussed at some length the erroneous idea that roentgen radiation in therapeutic doses is dangerous to the eye. At that time an analysis of the clinical and experimental data for the first thirty years of the twentieth century led us to the following unescapable conclusions:

1. The eye accustomed to the acceptance of light is, as a whole, less sensitive to roentgen rays than is the skin, even when large doses are indiscriminately applied.

2. The cornea of the eye is less sensitive to roentgen rays than is either the conjunctiva or the eyelid, and the iris is less sensitive than is the cornea.

3. The adult crystalline lens is remarkably insensitive to roentgen rays, but, while the cornea, conjunctiva and iris are only slightly sensitive in young or immature animals, the immature crystalline lens is more sensitive.

4. Exposure to roentgen rays sufficient to produce damage in the cornea or the lens leaves the retina unaffected.

These conclusions were borne out by experimental work on rabbits and have been reiterated by many writers on this subject.[2] Our

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 27, 1948.

1. Jones, J. W., and Alden, H. S.: Roentgen Ray Treatment of the Eye: Effect of Fractional Doses in One Hundred Cases; Preliminary Report, Arch. Dermat. & Syph. **43**:92-98 (Jan.) 1941.

2. (*a*) Borak, J.: X-Ray Therapy of Inflammatory Diseases, Am. J. Ophth. **26**:1170-1174 (Nov.) 1943. Foy, H.: Radiotherapy in Lesions of Eye, Tr. Ophth. Soc. U. Kingdom (pt. 1) **59**:458-463, 1939. (*b*) Schlaegel, T. F., Jr.: Ocular

experiences in the last fifteen years have clearly supported these statements and in addition have produced an enthusiasm for the therapeutic effects of roentgen rays on corneal ulcer.

Since the publication of our first report in 1941 on the treatment in 100 cases, the world has experienced a universal war and has entered on what some please to call "the atomic age." Since the explosions of the atomic bombs in Hiroshima and Nagasaki the effects of gamma rays on the human body have become common knowledge. The observations on the survivors of these bombings have enhanced medical knowledge of intensive group irradiation and have, in effect, substantiated existing understanding of the results to be expected from gamma radiation. Larkin [3] estimated that there was 473 r of gamma radiation per square centimeter at a little less than a mile from the center of the explosion of the atomic bomb at Nagasaki, and, since 500 r of general radiation will kill, it was as expected that those within this area and in buildings or rooms where there was reflected radiation died. Some of those who received such radiation on only half the body recovered and exhibited tissue changes which varied in severity in proportion to the known radiosensitivity of those tissues. All patients had some destruction of the hemopoietic system, with development of aplastic anemia; most patients had a partial epilation of one side of the scalp, and a few had testicular changes. They presumably recovered from these effects, with residual radiodermatitis. In no instance were there any ocular changes which were not obviously due to ultraviolet radiation or heat burns of the conjunctiva or cornea.[2b] There has been one conversational report of the occurrence of a cataract, but this has not been confirmed.[2b]

These findings support the observations of Desjardin [2c] and of Charteris,[4] the latter's experience being that damage of the lens is a rarity with 1,500 r and a certainty with 2,800 r. The observations also support Callaway [2d] in his findings on experimental damage from roentgen rays—that tissue recovery is complete after exposure to 300 r

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Histopathology of Some Nagasaki Bomb Casualties, Am. J. Ophth. **30**:127-135 (Feb.) 1947. *(c)* Desjardins, A. U.: Action of Roentgen Rays and Radium on Eye and Ear: Experimental Data and Clinical Radiotherapy, Am. J. Roentgenol. **26**:639-697 (Oct.); 787-819 (Nov.) 1931; Trends in Radiotherapy, Proc. Staff Meet., Mayo Clin. **13**:97-102 (Feb. 16) 1938. *(d)* Callaway, J. L.; Moseley, V., and Barefoot, S.: Effects of Roentgen Ray Irradiation on Testes of Rabbits: Possible Harmful Effects on Human Testes from Low Voltage Roentgen Ray Therapy, Arch. Dermat. & Syph. **56**:471-479 (Oct.) 1947.

3. Larkin, J. C.: The Distribution of Radiation in the Atomic Bombing of Nagasaki, Am. J. Roentgenol. **55**:525-532 (May) 1946.

4. Charteris, A. A.: Radium Treatment of Rodent Ulcer Near Eye, Am. J. Roentgenol. **44**:737-746 (Nov.) 1940.

and partial after that to 1,000 to 1,200 r, and that permanent damage results after exposure to 1,500 r or more, the damage being proportionate to the dose.

Since 1933 we have treated well over 300 patients with corneal ulcer referred by ophthalmologists, with gratifying results. During this period, and especially during the first few years, we used roentgen therapy for a number of other diseases of the eye, such as blepharitis, conjunctivitis, trachoma, corneal granuloma and keratitis. But, as was previously stated,[1] the results were not sufficiently encouraging to warrant the use of radiation in these diseases except under unusual conditions, since it appeared to offer no advantage over ordinary ophthalmologic treatment.

METHOD OF TREATMENT

For all these patients our technic has been as follows:

The roentgen radiation was obtained by means of mechanical rectification and a water-cooled Machlett tube. We employed 120 peak kilovolts and 6 milliamperes, with a tube-target distance of 8 inches (20 cm.), without filtration. This apparatus produced 160 r per minute. The eyelids were held open by an assistant, the patient looking directly at the filament light of the tube, and the surrounding area was shielded well with lead foil. For the past eight years we have used a one-half inch (1.3 cm.) brass tube as an application medium, without lead shields, with satisfactory results. Most patients received 70 to 80 r (one-quarter erythema dose) at weekly intervals; a few persons, with acute, painful corneal ulcers, received 120 r at the initial dose and 80 r for subsequent doses. To only 3 patients did we give more than twelve such doses; 2 had blepharitis and 1 a severe recurring corneal ulcer. The average number of treatments was five, given at weekly intervals.

The eye is made up of many tissues, most of which are of epithelial type of an extremely specialized nature. It is reasonable to assume that these tissues will react to atomic radiation in a manner similar to that of other epithelial tissues. Just how the roentgen rays produce salutary effects on inflammatory tissue is not clearly understood. It is well known that radiation produces some cellular destruction, even in the smallest doses, and that such destruction is in direct proportion to the immaturity of the cells. The highly specialized nature of the corneal epithelium and the crystalline lens makes these tissues, as well as the retina, more or less radioresistant. But in ulceration of the cornea and bacterial infiltration with edema and inflammation, new and immature cells become involved in the protective mechanism, and pain and discomfort close the eye as a protection against further injury. Since it is well known that superficial inflammation of epithelial tissues, characterized by infiltration of leukocytes, especially lymphocytes, is susceptible

to roentgen radiation in proportion to the degree of infiltration,[5] roentgen ray treatment should be of benefit without the danger of damage to normal tissue. Actually, our clinical experience has shown this to be true.

Sufficient time has now elapsed for us adequately to evaluate any late changes that may occur to the eye from roentgen radiation.

For 159 patients with diseases of the eye treated prior to 1943, the average total dose of roentgen radiation given to the eye was 252 r. This dose was, in most instances, salutary in its relief of the disease and is well within the limits of safety to epithelial tissue. Over 60 per cent of these patients have been examined carefully with the slit lamp since completion of their treatment, and no evidence of change leading to a cataract has been discovered. One patient in this series received further roentgen ray treatment from other sources, in a quantity and quality that is unknown. This woman, with a thyrotoxic condition, had a resistant case of blepharitis. She insisted on further roentgen ray treatment, against our advice. Contritely, she returned later to her ophthalmologist, having received little benefit, having refused treatment for her thyrotoxicosis and presenting a mild lenticular opacity. Such a result could hardly be blamed entirely on the roentgen rays, but must be considered due at least partly to her lack of cooperation.

Sometimes the effect of roentgen ray treatment on an infected corneal ulcer has been spectacular, and many patients prepared for enucleation have been saved the loss of an eye. The following case is an example:

On March 3, 1938, Mrs. R. A. R., a housewife aged 31, consulted an ophthalmologist with urgent advice from her physician that she have her right eye removed. A chip of wood had injured the globe four weeks previously, and the intensely inflamed, edematous and ulcerated eye was giving unbearable pain. There was no vision and little light perception. The ophthalmologist had no hope that vision would be saved but had suggested roentgen ray treatment in an effort to avoid enucleation of the eye.

On March 3 the patient was given 78 r directly to the open eye. This dose was repeated on March 7 and again on March 11. The pain gradually lessened, and the patient's condition was much improved. On March 16, 78 r was again given. Light perception was present; the pain was relieved and edema lessened. On March 26, when the ulcer was almost healed and vision was returning, 78 r was given. During this period and subsequently the patient received routine ophthalmologic care and nursing. Heavy corneal scarring resulted, but now, ten years later, the eye has normal external appearance and 20/100 vision, with no evidence of lenticular change.

In the treatment of infected corneal ulcer of exogenous causes (i. e., trauma or foreign bodies) we have had our best results, and so for all practical purposes we have in the past few years limited our roentgen therapy to lesions of this type. We have in no instance treated any

5. MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in Treatment of Diseases of Skin, ed. 4, Philadelphia, Lea & Febiger, 1946.

patient with ocular disease except on the request of the ophthalmologist. We wish to emphasize that the use of roentgen therapy for diseases of the eye is of value only when used with the full cooperation of the ophthalmologist, and good results are obtained only with simultaneous good ophthalmologic care of the patient's eye.

We, then, can repeat our conclusions arrived at in the original paper:

1. The dermatologist, owing to his ability to use roentgen rays in small superficial doses, can aid the ophthalmologist in the treatment of inflammatory diseases of the eye.

2. Roentgen rays used carefully and properly will not produce any damage to the eye.

3. Roentgen rays used carefully and properly will relieve the intense pain and the inflammation of corneal ulcer in the majority of patients.

4. The treatment of blepharitis is not materially aided by the use of roentgen rays.

5. Roentgen rays are of paramount value in the treatment and cure of corneal ulcer.

We can add that repeated examinations with the slit lamp of eyes treated in the past fifteen years with roentgen radiation, in proper doses, has not revealed a single case of cataract due directly to such treatment.

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ROLE OF SPECTACLE LENSES IN PRODUCTION OF CUTANEOUS CHANGES, ESPECIALLY EPITHELIOMA

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IN HIS diagrammatic illustration plotting the localities affected by epithelioma of the face, Andrews [1] placed an incidence of over 40 per cent in the region with which this paper deals. For a number of years one of us (E. F. C.) has been interested in the occurrence of these growths, together with keratoses and chronic scaly dermatitis, in the spot or band of light engendered by refraction of rays emerging from the lower edge of spectacle lenses of various sorts. Differing in degree according to the mounting and type of lens employed, there is a varying zone of light apparent on the cheek, often converging into an arc with the concavity up or appearing as a brightly luminous spot. This focal area remains rather definitely localized despite its changing relationship to the source of light. To obtain the sharpest focusing effect, this light must be directly above the patient's uncovered head or in front of or behind that point, provided that its rays can strike the upper edge of the lens at the proper angle to refract to the cheek.

In our investigations it was found that certain types of spectacle frames were especially responsible for transmission of light and its focusing on the skin below the lower edge of the lens (fig. 1). These were, above all, the rimless spectacles with lenses of round or elliptic

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1. Andrews, G. C.: Diseases of the Skin, Philadelphia, W. B. Saunders Company, 1930, p. 936.

outline. While the character of the lens—whether plus or minus; thick or thin; sphere, cylinder or prism—was responsible for a certain difference, nevertheless the same principle existed in all cases in which a wholly or partially unobstructed rim of the lens was present. The route traversed by the light beam could be blocked readily at either edge by the use of a lacquer employed by the optical trade and known as rim black.® When carefully applied either to the upper or the lower rim of the lens it was hardly noticeable and the rays we deemed important in their effects on the skin were entirely cut off. All that remained was a diffused reflection, a lighting-up of the skin back of the lens and also of an area somewhat below the beam of refraction just referred to, definitely

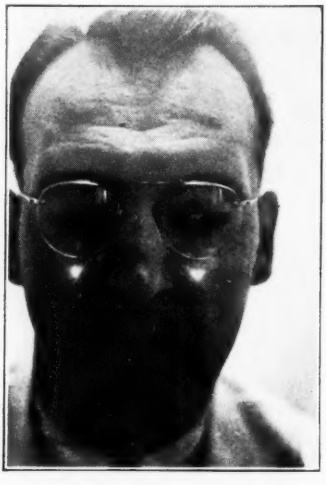

Fig. 1.—Typical focus of rays from overhead light condensed by passage through spectacle lenses in a somewhat vertical direction.

caused by the mirror-like effect of the posterior surface of the lens, which cast light on the area mentioned. This reflection could be readily blocked by lightly stuffing cotton, paper or any other material which does not transmit light between the upper portion of the lens and the upper eyelid, care being taken not to overlap the upper rim if one wished the refracted beam to persist. Then, if the rim black® was in place, all light would be cut off save that transmitted through the thickness of the lens in an anteroposterior direction, which had no focal effect on the skin immediately behind it, as the optical glass is prepared to condense the rays from this direction on the retina, with the help of the natural lens.

Since we seemed to have traced the route of the visible beams involved, the question as to heat effects caused by the rays remained. Infra-red and light rays are said to be refracted similarly. Employing thermometers with mercury columns and also thermometers containing an alcoholic fluid commonly used for recording atmospheric heat changes, we took the temperature of the cutaneous areas on which the beams of refracted light focused from, in turn, sunlight, a 500 watt photoflood lamp and a 100 watt mazda® bulb. The zone of reflection outside the refracted focus was similarly tested. Some trials were made with the glasses on a human face; others, on a black mask, by use of which it was intended to avoid the influence of body temperature. While the actual temperatures varied, it was found that sunlight invariably produced in the course of one minute a rise of temperature in the focal area to as much as 3 degrees F. more than that obtained in the nearby zone of merely reflected light.

When tests were made with sunlight, the glasses being mounted on a mask, the results were as follows:

Temperature Within the Focal Area	Temperature Outside the Focal Area but in the Zone of Reflection
91.0 F.	89.0 F.
91.6 F.	90.0 F.
92.0 F.	90.0 F.

Sunlight, with spectacles on the human face, invariably produced a higher temperature in the focal area than outside it. Thirteen tests of a minute each on 3 different persons gave readings of from 1 to 3 degrees F. higher in the focal area. These tests were made in warm weather.

The photoflood lamp, at a distance of 4 feet (120 cm.) directly above the head, with spectacles mounted on a black mask, gave the following results in one minute:

Temperature Within the Focal Area	Temperature Outside the Focal Area but in the Zone of Reflected Light
94 F.	91 F.
92 F.	90 F.
93 F.	90 F.

The basic variations in temperature readings as a whole were due to the fact that the tests were done on different days and at different times of day. The thermometer was always held against the skin or the mask after being shaken down or cooled by other means before each test.

When the 100 watt bulb was used, there were no significant changes in temperature in the two zones, so that method was soon discontinued.

Tests made with rim black® on the upper edge of one lens of a pair of rimless spectacles with lenses of equal power gave differences of from 1.6 to 2.2 degrees F., with the higher reading under the unobstructed lens. The thermometer was placed in the sharp focus of one side and in a corresponding position on the other side.

When the rim black® was on only the lower edge of the lens, one minute readings of 1.3 degree F. difference were noted, while a four minute exposure succeeded in raising both figures higher (98.8 and 96.4 F.) with the difference amounting to 2.4 degrees F., the figures being higher both times in the focal area. The heat rays, therefore, as well as the visible rays, can be blocked at their points either of entrance into or of emergence from the glass.

When lenses without rims but with a different lower margin (semi-hexagonal), including a straight (horizontal) lower edge, were employed, there was less focusing effect and difference in temperature. In some such lenses the beam was converged to two lateral areas and not downward, this effect being due to styling of the rim. The rims were ground in conformance with the usual custom, as the glasses are worn by the vast majority of users. The rims did not have highly polished edges.

In order to ascertain the percentage of ultraviolet rays passed through spectacle lenses in the direction described, we made use of a spectrophotometer.[2] In this apparatus the ultraviolet rays are produced by a hydrogen discharge tube. Since the testing chamber at our disposal did not admit an entire breadth of lens, we employed the middle portion of a glass sectioned horizontally in thirds, with the edges ground smooth. This was held so that the rays were directed against the upper edge, the lens being turned to a horizontal position. The lenses used were — 2.25 D. and + 3.75 D. In tests of the carcinogenic rays from 2,900 to 3,200 angstrom units, there was no transmission of ultraviolet radiation below 3,100 angstrom units, while but 13 per cent of the output was transmitted at 3,200 angstrom units. Since this test was made through but one third of the length of the usual path through the glass, it is thought that the full breadth would further reduce the quantity of ultraviolet radiation. In the same apparatus, with the rays directed against the anteroposterior thickness of the same lens, from 55 to 65 per cent of the ultraviolet radiation was transmitted, the proportion depending on the thickness and type of lens employed.

2. Beckman photoelectric quartz spectrophotometer.

Since ultraviolet light seemed to be largely eliminated, it may not play an important part in the production of these cutaneous changes. Coblentz,[3] in a recent article, mentioned experimental data indicating that excessive, often repeated doses of ultraviolet radiation were possibly responsible for the production of cancer of the ears of mice. He called attention to the fact that the work of Blum [4] had been on laboratory animals and that the investigator had felt it unwise to apply the findings to man. Nevertheless, Coblentz pointed out the implication of the danger in the overuse of sun lamps, which suggestion may have a bearing on our present subject.

In the following series all the patients were white, none but Caucasians having been observed to exhibit the changes under discussion.

REPORT OF CASES

CASE 1.—A. M. P., a man aged 47, first seen by us on May 2, 1927, presented a horizontally linear growth of four to five years' duration. It was located on the right cheek about 2 cm. below the line of the upper lid. No scar or known trauma had antedated its appearance. A scaly, reddened, infiltrated area had developed in a slightly curved transverse line with its convexity downward. This, in turn, had given rise to a linear ulceration, framed in small, typically pearly nodules. Bleeding occasionally occurred. The patient had worn glasses since the age of 18. His correction was such that the sharpest focus usually fell on what later became pathologic tissue. No actual contact could take place between the diseased skin and the spectacles at this point. While the patient had worn various styles of frames, a rimless type was being used at the time of his attendance and had been worn for some time previously. Before destruction of the lesion, a section of material taken with a biopsy punch revealed the condition to be basal cell cancer.

CASE 2.—H. C. B., a man aged 51, who was first observed by us on Jan. 28, 1936, had a rounded growth on his right cheek, 0.6 cm. from the ala of the nose. It was the size of half a split pea, with a small central ulcer. The patient had worn rimless glasses for many years and was an outdoor sports enthusiast. With much exposure to sunlight, a few pigmented keratoses had developed at the temples but had appeared at a later date than the mark on his check, to the best of his recollection. His spectacles had always been kept adjusted so that they did not contact his cheek, he said. The beam of an overhead light focused exactly on the suspected lesion. This was clinically an epithelioma, the type being undetermined, as no biopsy was performed before destruction of the growth.

CASE 3.—C. H. E., a woman aged 49, had a small growth located 0.5 cm. below the lower edge of the glasses she wore. It had been present for more than a year.

3. Coblentz, W. W.: Experimental Production of Cancer of the Skin by Ultraviolet Radiation, J. A. M. A. **136**:1040 (April 17) 1948.

4. Blum, H. F.: Photodynamic Action and Diseases Caused by Light, American Chemical Society Monograph Series, no. 85, New York, Reinhold Publishing Corporation, 1941, p. 254.

The patient was fond of gardening and exposed herself to the sun, without much protection of the head in summer. Even in a moderately subdued light there was to be noted a well defined zone of focus, in which the lesion was located. The patient had worn rimless glasses for several years. The growth proved to be a basal cell epithelioma.

CASE 4.—Mrs. G., a woman aged 45, with a sensitive, freckled skin, had a rounded nodule just above the lower edge of the right spectacle lens when seen on June 5, 1938. The growth had a translucent quality, with a telangiectatic surface, and was deemed an epithelioma, although biopsy was refused. This lesion was strikingly illuminated by a focused ray when sunlight fell on the patient's face. She had worn glasses, mostly of the type with metal rims which did not entirely obscure the edge of the lens, for many years.

CASE 5.—H. B. M., a man aged 47, first seen by us on Nov. 28, 1933, had a tranversely linear growth with a gutter-like median ulcer. It had been present

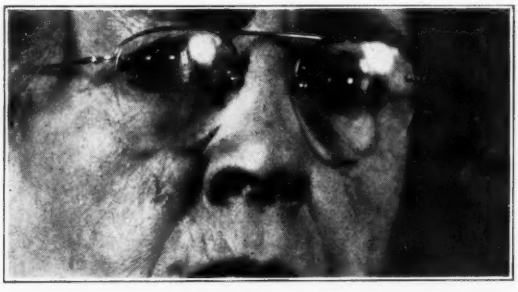

Fig. 2 (case 6).—Bilateral changes in the skin from focused light. A basal cell cancer is present on the right cheek and the scar of a former lesion on the left cheek.

for about five years, the edges at the time of examination showing typical "rolling." Bleeding sometimes occurred. The patient constantly wore spectacles, which did not touch the affected region. Sunlight and overhead light produced an arc-shaped illumination, with the convexity downward, enveloping the growth. The neoplasm proved to be of the basal cell type of cancer.

CASE 6.—Mrs. W. F., aged 56, was referred to us on Sept. 21, 1931, by an ophthalmologist. A nodule the size of a grain of wheat had appeared on the left cheek 1.5 cm. below the lower rim of her spectacles. Observation under an overhead light showed a beam focused sharply on the affected area. The papule was opalescent, and some telangiectasia existed at its margin. The growth was destroyed, a smooth, whitish scar being left when the patient was seen in the following December. On Aug. 22, 1947, the patient returned with a larger growth symmetrically placed on the right cheek (fig. 2). Again her rimless glasses were noted to focus a beam of light on the tumor. A biopsy confirmed our impression that the growth was a basal cell cancer, which was subsequently destroyed.

CASE 7.—H. W. W., a man aged 64, when seen on Oct. 8, 1946, had symmetric red spots of equal size about 0.5 cm. below the centers of his "back-set" type rimless spectacles. These lesions had been present for about a year. In sunlight and under electric ceiling lights the areas were brightly illuminated. There was practically no infiltration, but there was slight scaling at times, and the diagnosis of chronic dermatitis of actinic origin had been made.

CASE 8.—J. H. R., a man aged 76, when seen on Oct. 22, 1943, presented chronically inflammatory, scaly lesions on both cheeks, each centered about 0.5 cm. below the lower edge of the spectacle lens. These areas each measured 1 cm. in diameter and presented thin, brown, crusted surfaces. Keratoses were present at the temples and in front of one ear. The lesions in question were of the same character, though, we believe, located and determined by the ray which beamed on them.

CASE 9.—E. Q., a man aged 43, a spectacled mechanic who frequently went bareheaded in summer, came to us in October 1947. There was bright, con-

Fig. 3 (case 11).—Biopsy of a specimen taken from the right side showed the growth to be a basal cell cancer. There is a scar of a former lesion on the left cheek.

centrated light at two points below the lower rims of his glasses, exactly where two nodules were located. These were pea-sized, though flattened. The right one, slightly larger than the other, proved on biopsy to be a basal cell epithelioma. Both were destroyed by electrodesiccation. This patient had worn rimless glasses at one time, but of his own accord had changed to a plastic frame. Even with this there was evidence of focusing action.

CASE 10.—M. G., a woman of 52, a patient of Dr. John F. Wilson, had an elevated, nodular, cystic lesion of the left cheek about 1 cm. below the lower arc of her spectacles. This had been present for about two years before she was seen in 1946. She had worn bifocal lenses for the past eight years. The lesion proved to be a basal cell epithelioma, which was destroyed by electrocoagulation. There were no keratoses or other evidences of premalignancy present. The growth described seemed to be located at the seat of focus of the light through her lens.

CASE 11.—C. E. M., a man aged 55, an executive, was first seen on March 11, 1942, because of a small growth 1 cm. below the lower rim of his spectacles

(fig. 3). In certain positions his rimless spectacles caused a bright focus on the sites of the appearances to be described. In a nearly corresponding position on the left side a scar of a formerly active lesion was noted. This had been successfully treated by irradiation in a midwestern city, and the patient had been told that it was a cutaneous cancer. The nodule on the right was firm and pea sized and exhibited a central crust and a translucent elevated margin. Sections from material taken with a biopsy punch from the lesion on the right cheek were found to exhibit characteristics of basal cell cancer. Under intensive irradiation the growth had entirely healed by June 1944.

CASE 12.—C. E., a man aged 61, had noticed red spots in areas of the cheeks just below the lower rims of his eye glasses for several months. It had been observed that when he spent much time outdoors while bareheaded these marks were especially bright. On examination, in September 1944, two reddish areas without sharp margination were noted in the sites mentioned. There was no infiltration; pressure failed to remove the color, and a light scale adhered to the surface. The patient's spectacles were rimless. There was no gross evidence of lupus erythematosus. The blood was found to be normal. The diagnosis was chronic actinic dermatitis.

COMMENT

Refracted light conducted from the upper to the lower rims of spectacle lenses is found to produce an elevation of temperature at the spot where it focuses on the skin. This focus is not always a perfect one and varies somewhat in shape and position, in direct accordance with changes in the source and with the movements of the person involved. This action is somewhat reminiscent of that of the lucite® devices and tongue depressors, for example, with which light can be "piped" around bends through refractile material without lateral spread.

Our special interest in the phenomenon is in its effect where it focuses on the skin, and 12 cases selected from a series are reported in which cutaneous changes were believed to have been caused by the heat or chemical rays conducted to the cheek by spectacle lenses—a "burning glass" effect.

The correspondence of the focal area with the cutaneous changes would seem to be more than a coincidence. Even though exposure to sharp focus is brief, if it is repeated habitually it may exert a positive effect.

It is believed that glasses without rims, which especially refract this beam, are largely responsible for these effects, but even this style of spectacles can be worn safely without structural change if rim black® is carefully applied to the upper or lower edges of the lenses.

Effects of actual contact of any part of the spectacles with the skin are not considered in this paper.

Dr. Daniel L. Turner, of the Department of Biochemistry of Jefferson Medical College of Philadelphia, assisted with the spectrophotometry required for this article; and J. Francis Cleary, of Keene and Co., Opticians, gave advice and furnished and mounted lenses.

Medical Arts Building (Dr. Corson).

1015 Walnut Street (Dr. Knoll and Dr. Luscombe).

527 Penn Street (Dr. Decker).

DISCUSSION ON PAPERS BY DR. ALDEN AND ASSOCIATES AND DR. CORSON AND ASSOCIATES

Dr. John Lamb, Oklahoma City: These are two very interesting papers on the effects of radiant energy on and about the eye. Opthalmologists are now aware of the value of roentgen ray and radium therapy of ocular diseases, and no one is better prepared to treat these structures with radiation than are dermatologists.

This procedure was looked on formerly with extreme conservatism because of reports of damage to the lens. But treatment with these agents has not been shown to produce any such effects on the human adult lens. Drs. Alden and Jones are to be congratulated on their excellent study of a larger series of cases over a long period to permit clinical determination of the total dose of roentgen radiation that the human lens can tolerate. I agree entirely with the conclusions drawn by them. For the last eight years my associates and I have treated patients with corneal ulcers, interstitial keratitis, early squamous cell epitheliomas at the limbal juncture, epithelial downgrowths following cataract extraction and recurrent pterygiums, all sent to us by ophthalmologists. We have not yet seen a cataract produced in the crystalline lens by either roentgen rays or radium in our small series.

The infected ulcers of exogenous causes have proved in our series also to have responded best to roentgen therapy. However, our dosage was limited to a total of 400 to 500 r given with 60 kilovolts unfiltered at a distance of 9 inches (22.8 cm.), 60 r at each treatment, with intervals of five days for the most acute cases and of a week for the less acute.

These excellent results are interesting to compare with the report of Illiff, of the Wilmer Institute at Johns Hopkins, in which beta radiation from 500 millicuries of radon was used. Illiff reported failures in 11 cases of corneal ulcers due to either staphyloccocic or mixed infections and drew the conclusion that the results were what would be expected, because irradiation hastened the breakdown of already damaged cells.

Two early epitheliomas of the limbal juncture were cured with 100 r of roentgen rays, filtered by 1 mm. of aluminum in two divided doses through a small cone to the lesions, followed by a total of seven hours of irradiation with half-strength 5 mg. radium plaque with 0.8 mm. brass filtration at a distance of 0.25 cm. This

treatment was given at one hour daily sittings; the cornea was kept moist by an isotonic solution of sodium chloride dropped into the eye every two or three minutes. I believe Drs. Alden and Jones have stimulated a new interest in irradiation of the eye by their fine contribution.

Dr. Corson's paper seems to me to be fundamental and may aid in explaining how sunlight causes carcinomatous changes in the skin. Findlay and Roffo claimed to be able to produce carcinoma in white mice and rats with repeated daily exposures to radiation from a mercury vapor—quartz lamp. However, Rothman and Bernhardt could not produce true cancer by this means, although there was some thickening of the skin in what they thought to be a precancerous condition.

In all these experiments with radiation from a mercury vapor—quartz lamp, one must be cognizant of the fact that the lamp operates at a relatively high temperature, so that a certain amount of infra-red radiation is emitted.

With Dr. Corson's suggestion that an increase in the temperature of the skin produced by heat (infra-red) waves may lead to cancerous changes in the skin, some experimental work must be done on the local effects of infra-red radiation on the skin. Perhaps both the increase in temperature and the ultraviolet rays are necessary to produce these neoplastic changes in the epithelium. I do not believe that in our part of the country light focused through spectacle lenses has much to do with malignant changes on the cheeks, since most of our outdoor workers wear broad hats, but I am sure that heat, reflected infra-red as well as ultraviolet radiation, and hot, dry winds have something to do with the increase of cutaneous cancer in our region. I believe that Dr. Corson's experiments with the spectacle lens and the increase in temperature of the skin leading to carcinomatous changes is an excellent piece of clinical research and one worth extension in laboratory study.

Dr. Anthony C. Cipollaro, New York: I am glad to have had the opportunity of hearing these two excellent presentations because they illustrate the importance of cutaneous measurements. If scientific data could be recorded numerically, it would be simple to express and follow scientific progress, as our chairman emphasized in his address.

Cataract is said to be caused by exposure to roentgen rays. However, ophthalmologists who have made such contentions have failed to present critical proof. It has been the consensus of those who have studied the problem that cataract has developed in patients who received roentgen radiation as well as in those who were never exposed to ionizing radiation. The cause of cataracts is not known. The dosage used by Dr. Alden and Dr. Jones is that ordinarily used for the treatment of common cutaneous diseases, such as eczema, acne and psoriasis, namely, 75 r at weekly intervals for a maximum of from eight to twelve treatments. Such doses are well tolerated by the normal adult skin and by the structure of the eyes. Will Dr. Alden's paper give dermatologists license to treat ophthalmic conditions? I hope not, but it definitely establishes the fact that it is safe to treat lesions of the eyelid, such as eczema and epithelioma, without fear of causing a cataract to develop.

I hope those who read this paper in the ARCHIVES do not start treating lesions of the eyes with roentgen rays when other methods can be employed.

Dr. Corson's paper was most instructive and stimulating. It is my idea that ultraviolet rays are absorbed by the lenses of the glasses. Therefore I do not see how cancer can be produced by the transmission of sunshine through the lens glass, because ultraviolet light rays will be absorbed by such glass. It may be that the combined infra-red and ultraviolet rays have an additive effect and thus cause cancer to develop in special locations and under special environmental conditions. The clinical and experimental evidences clearly confirm the contention that ultraviolet light is definitely carcinogenic. Infra-red rays are not necessary in the causing of experimental cancer.

DR. CORNELIUS FERD LEHMANN, San Antonio, Texas: Dr. Corson's paper brings up the consideration of an important subject in my mind. It particularly concerns us who live in that belt of the United States where sunlight plays an important part in the production of cutaneous cancer. I have often conjectured as to why so many people in our section have cancer. Does the type of person who is a farmer or a mariner or a rancher have a certain predisposition? So many of these people are blond, red-skinned persons, who burn easily. Is it the habits of these people? They either have too much of or lack something. I have experimented with preparations of vitamin A, creams and ointments, for example. Just now I have been employing a trick in handling these people. Most of them don't have running water and consequently do not wash frequently, and so I tell them that they have to use creams and lotions that must be put on after washing the face so that they will use soap and water. The creams and lotions may be of value, but it is my desire to get the patients to wash off the skin. I feel that there is need of research work on this matter, and I wish I were equipped to do it. What is the possible photodynamic effect of the sebum of the skin? What possible chemical change may exist? The sites of epithelioma on the face may be explained on an anatomic basis. Although I do not believe that Dr. Corson has proved his point entirely, the value of his paper is the effort to bring out facts concerning epitheliomas and determine what causes them. This question is important to us who live in a section of the country where sunlight plays a large part in producing these growths.

DR. PAUL E. BECHET, New York: I was greatly interested in the paper by Drs. Alden and Jones for the reason that about eighteen years ago I had observed in private practice a woman, aged 62, who had had a growth on the lower left eyelid for fourteen years. I saw her for the first time on March 7, 1930, at which time the entire lower lid was covered by an epithelioma, which had already destroyed a large part of it but had left the eye intact. The lid was drawn down as much as possible with adhesive tape, and unfiltered roentgen rays were administered through an aperture in lead foil. The shield covered only a part of the eyeball, the lower third of it being exposed to the rays. Three doses of 750 r each were given in a period of six months, making a total unfiltered dose of 2,250 r. No eye guard was used because of the extensive ulceration of the lower lid and the fact that an ophthalmologist had told me that he had observed serious ulcerations of the eye after a guard had been used. The patient was

presented before the New York Dermatologic Society (ARCH. DERMAT. & SYPH. **32**:347 [Aug.] 1935) five years later. She had remained entirely well, with an excellent cosmetic result, and a careful examination by an ophthalmologist revealed that the eye was normal.

I saw the patient ten years later—fifteen years after the last irradiation—at which time the eye was still normal, with no recurrence of the extensive epithelioma. The results in this particular patient support the views of Drs. Alden and Jones.

DR. JOHN BELISARIO, Sydney, Australia (By invitation): I appreciated hearing of these interesting cases. For many years it has been my desire to attend a meeting of the American Dermatological Association. It has been a great pleasure to gratify this desire at last, and I wish to thank you for the high compliment and honor you have paid me in having me here.

I was extremely interested in the subjects just discussed. Dr. Alden's paper was thought provoking and stimulating to us who use roentgen rays. In the past, people considered that the use of fractional doses of roentgen rays to the eyes was extremely dangerous. I am pleased to hear what Dr. Alden said in regard to the subject because I have used roentgen rays for superficial conditions a great deal. We in Australia have not, as a rule, given more than 4,500 r in hyperintensive dosage. We have never seen any trouble in the eye which was definitely attributable to that dosage, but I have always been a little doubtful. I should like to ask Dr. Alden whether he stated that damage would occur after exposure to 18,000 r.

DR. ALDEN: Yes.

DR. BELISARIO: With hypertensive doses it would be possible to produce damage. My associates and I have treated a number of lesions about the eyes with radium by the Manchester technic. The standard dose is 6,000 r of gamma rays. We have felt on occasion that some cataracts, observed five or ten years later, might have been due to this treatment. We do not use radium around the eyes any more, but we do use roentgen rays.

The following method gives complete protection to the eye. I use a piece of lead foil 1 mm. thick as a screen to protect the eye. It is 2 to 3 cm. broad and 5 to 8 cm. long. After the eye has been cocainized the screen is impressed over the eyelid not being treated and under the lid to be treated. The free end is then strapped to the forehead or cheek and a screen placed over the lesion. Roentgen rays can then be applied, and the eye is fully protected. This has proved an extremely successful method. The total dose usually applied to basal or squamous cell carcinoma is 2,000 to 3,500 r in one sitting. As Dr. Cipollaro said, ultraviolet rays are absorbed by glass. This observation brings me to a point on which I should be grateful for any advice. I have been working on a subject which has to do with ultraviolet light. In the range of the electromagnetic spectrum, the rays with shorter wavelengths are the most penetrating until one reaches the ultraviolet rays, from which point those of longer wavelength are more penetrating. When the infrared rays are reached, penetration is again found to be greater with rays of shorter wavelength. Why does this phenomenon exist?

In conclusion, I think these papers will do a great deal for future problems of treatment. In regard to ultraviolet rays, which play a large part in the production of keratoses and cutaneous carcinomas, I can assure you that Americans in certain sections have no worse problem of sunlight than we have in Australia. We have the highest incidence of cutaneous cancer in the world, and the craze for sunbathing plays a part. We see many carcinomas around the eyes; however, I don't know whether the incidence is greater in people who wear glasses or not. I shall check up when I return.

DR. MARTIN F. ENGMAN JR., St. Louis: Dr. Engman Sr. got his first x-ray machine in 1904. He bought 200 mg. of radium in 1917. Our office has thus had a long experience with roentgen rays and radium, particularly in treatment of lesions about the eyes. We have never felt any fear of treating inflammatory lesions and tumors around the eyes with radiation, using reasonable precautions and conservative dosage. In our experience, apparently the eyes have considerable resistance to radiation, as has been pointed out in Dr. Alden's paper. Roentgen radiation is very useful in the treatment of eczema of the eyelids, and also in that of disseminated neurodermatitis, which involves the eyelids. These diseases are recurrent, and it may be necessary to treat repeated attacks. Thus, there may be the possibility of a medicolegal problem. Juvenile cataract may occur spontaneously, particularly in cases of disseminated neurodermatitis. The roentgen ray treatment could conceivably get the blame.

I think Drs. Alden and Jones's paper is of great medicolegal value.

DR. HERBERT S. ALDEN, Atlanta, Ga.: It is comforting to have the discussers substantiate the findings we have presented in our paper. I appreciate Dr. Belisario's comments. I should like to say in regard to Dr. Cipollaro's statement that dermatologists probably will not assume the responsibility of treating ophthalmologic diseases. The invitation will have to come from the ophthalmologists. In the early days, the use of roentgen radiation came through Drs. Clay and Baird, ophthalmologists. They were criticized by ophthalmologists for even suggesting such treatment. They are now getting good results, and the ophthalmologists are becoming interested in this problem. There is no question that roentgen therapy will save the eye from enucleation in some cases of corneal ulcer. I do hope that, more and more, dermatologists will be able to treat with roentgen rays ophthalmologic diseases in limited degrees, at the request of the ophthalmologist. I appreciate the discussion.

DR. EDWARD F. CORSON, Philadelphia: Apparently Dr. Cipollaro thought that it was probably infra-red rays which were responsible for the neoplasms discussed in our paper. I am reasonably sure that ultraviolet light can also be transmitted through ophthalmic glass. I was greatly surprised, in looking up the matter of the various glasses which are produced commercially, to find such a vast number of varieties. I agree that common window glass cuts out ultraviolet light; ophthalmic glass, however, has different properties. The spectrophotometer aided us in determining the fact that in some cases ultraviolet rays are transmitted. We were concerned entirely with clear glass, not tinted. Dr. Bechet spoke of superficial burns as the result of the use of infra-red rays. It is this sort of thing,

repeated many times in the same location, which gives rise to the more serious consequences. I appreciate Dr. Belisario's discussion. We realize that epitheliomas develop on all parts of the face. We were centering attention on the area below the spectacle lens, which sometimes is protected from direct sunlight by the configuration of the face. One would not be likely to have carcinomatous changes, or even signs of cutaneous irritation, there unless some injury was being received from a particular source.

I wish to add my thanks to Dr. Alden's for the full discussion by the members and guest.

ESTROGENIC OINTMENTS

Cutaneous Effects of Topical Applications of Natural Estrogens, with Report of Three Hundred and Twenty-One Biopsies

JOSEPH J. ELLER, M.D.

With the Collaboration of

WILLIAM D. ELLER, M.D.

NEW YORK

THIS study was undertaken to determine whether any changes in the skin could be produced by topical application of hormone-containing ointments.

MATERIALS AND METHODS

The study was conducted on 36 persons, of whom 30 were men and 6 women.

GROUP 1A.—This group consisted of 9 postmenopausal women, most of whom fell into a rather advanced age group, that from 51 to 79 years.

GROUP 1B.—This group consisted of 5 men, all over 55 years of age. These two groups were treated in an identical manner with an ointment containing 7,500 international units per ounce (242 international units per gram), as follows:

Beneath each scapula a 10 by 10 cm. area was marked out as the test area. On one side a 4 Gm. portion of the ointment, containing a total of approximately 960 international units of estrogens, was spread over the test area and covered with a square of glassine® paper. Over this a gauze pad was taped in place. As a control, the identical procedure was followed on the corresponding area of the skin on the other side, using a 4 Gm.. portion of the same ointment base, which, however, did not contain the estrogenic substance. After two weeks of this treatment, 1 male and 1 female patient had a contact dermatitis, which was caused by the wartime adhesive plaster used. These 2 patients were dropped from the series after twenty days of treatment.

This investigation was facilitated by a grant and a supply of testing materials from Bonne Belle Inc., Cleveland.

Read at the Sixty-Seventh Annual Meeting of the American Dermatological Association at Murray Bay, Quebec, Canada, June 5, 1947.

The Research Committee of the New York City Hospital granted us permission to conduct this investigation. The biopsy specimens were cut, prepared and studied in the Department of Pathology (Dr. James R. Lisa, Director) of the New York City Hospital, in conjunction with the Department of Dermatology. Dr. Fred D. Weidman and Dr. Lawrence W. Smith studied the slides and reported their opinions, which are incorporated in this paper. Dr. Joseph W. Goldzieher and Dr. Meyer H. Slatkin, resident and assistant resident, respectively, at the New York City Hospital, applied dressings, took biopsy specimens, made vaginal smears and assisted the pathologist of the hospital in conjunction with this work. Margaret M. Skelley, R.N., and Elizabeth Anderson, R.N., applied over 1,200 dressings and innumerable inunctions during the course of this study. Dr. John H. Nolan granted us permission to make studies on certain of his patients.

GROUP 2.—This group consisted of 7 aged women and 1 aged man. They were treated by inunction for approximately one minute with the same ointment, containing 960 international units per 4 Gm. portions. On 3 of these patients a corresponding 10 by 10 cm. area of subscapular skin was used, and for the remaining 5 patients a similarly sized area on the anterior surface of the thigh was chosen. Each inunction was carried out with a 4 Gm. portion of ointment. Control inunctions were performed simultaneously on the corresponding areas on the other side of the body; for 5 patients white petrolatum was used, and for the remaining 3 patients, the same vehicle was employed except that it was estrogen free.

GROUP 3.—This group consisted of 5 aged women. These patients were treated by inunction of a 10 by 10 cm. area on the thigh with an ointment containing 15,000 international units per ounce of ointment, equivalent to approximately 1,935 international units of estrogen per 4 Gm. portion. As a control, white petrolatum was used on a corresponding area on the other side of the body.

GROUP 4.—This group consisted of 4 young women, each of whom was carefully examined for any sign of endocrine dysfunction. The menstrual cycles were normal in each case. The subscapular area was used; application, as in group 1, was used in 1 case and simple inunction in the remaining 3 cases. A 4 Gm. portion of ointment containing 960 international units was used as the test material, and the same quantity of estrogen-free ointment was used as for the control.

GROUP 5.—This group consisted of 5 aged women who were originally in group 1 and who were restudied after a month's interval. The new test area in this group was the anterior surface of the thigh. Inunction of a 10 by 10 cm. area with white petrolatum containing 1,935 international units per 4 Gm. portion was rubbed on the skin for one minute.

Inunctions and dressings were done daily at about the same hour. The area was wiped off once with ether before the fresh material was applied, except in groups 3 and 4, in which any remaining material was gently wiped off with dry gauze.

A base line biopsy of the test area was made before the beginning of the treatment, and biopsies of both control and test areas were made every ten days thereafter. In a few instances the fifty day biopsy was omitted.

Biopsy specimens were taken with a 5 or 6 mm. Keyes punch after local anesthesia had been induced with a 1 per cent solution of procaine hydrochloride. The tissues were fixed in a 1:5 dilution of Bouin's solution for eight to twelve hours, after which they were cut in half and embedded in paraffin. Embedding, sectioning and staining of the tissues were carried out by the same technician. Sections were prepared with (*a*) hematoxylin and eosin; (*b*) the Weigert technic for elastic fibrils, with Van Gieson's method and hematoxylin as a counterstain, and (*c*) Ranvier's picrocarmine stain (for keratohyalin) with a very light counterstain with hematoxylin.

At the conclusion of sixty days of treatment, vaginal smears were taken on 17 of the postmenopausal women and stained with Shorr's single differential stain.

Examination of the vaginal smears showed changes of such a minor degree that a special grading was necessary. Grade 0 represented a completely normal smear, with numerous polymorphonuclear leukocytes, debris and small ovoid epithelial cells with large nuclei. Grade 1 smears showed only disappearance of the leukocytes; grade 2 smears, disappearance of the leukocytes, an increase in the size of the epithelial cells, a relative decrease in the size of the nuclei and the appearance of a few polygonal, but as yet entirely uncornified, cells, and grade 3 smears, polygonal cells, chiefly, with a rare pink (cornified) cell appearing. Even

when the greatest degree of change was apparent, as in the grade 3 smears, the very immature, ovoid epithelial cells had not entirely disappeared.

The estrogenic material used was a natural estrogenic substance derived from the urine of pregnant mares, which on assay was shown to contain about 85 per cent estrone, with small quantities of estradiol and related hormonal substances. This estrogen was used in two potencies, namely, 7,500 international units per ounce (242 international units per gram), and 15,000 international units per ounce (484 international units per gram) in an ointment consisting of hydrous wool fat U. S. P. and white petrolatum, with small quantities of cetyl alcohol and cholesterol alcohols. The estrogen was also incorporated into white petrolatum with a potency of 15,000 international units per ounce.

RESULTS

1. *Changes in the Control Skin.*—In none of the 10 cases in which estrogen-free white petrolatum was used as the control inunction was any change in the skin noted. The slight massage necessary to facilitate inunction (about one minute) did not alter the histologic appearance of the skin. Of the cases in which the estrogen-free ointment was used as the control (either by application or by inunction) minimal epidermal changes occurred in 11 and doubtful changes in 4. Thus, in 57 per cent of the cases a minimal effect due to the estrogen-free ointment was noted. Such changes as did occur were not noted before forty to fifty days, except in 2 cases, in which they were observed at the end of thirty days. These changes consisted of (*a*) a slight waviness and a slight increase in cellularity of the basal layer and (*b*) a small, but perceptible, increase in the thickness of the epidermis. These were the most pronounced changes that occurred, and they showed no progression after their first appearance. It was observed that the most prominent changes were induced in cases in which the glassine® paper application method was used, rather than in those in which the inunction method was employed. This manifestation is probably due to the fact that the application method, by the use of glassine® paper, assured a continuous twenty-four hour a day contact.

2. *Changes in the Estrogen-Treated Skin.*—As a result of these experiments, it was found that estrogens exerted a definite and consistent proliferative effect on the epithelium of the skin, as judged by histologic criteria. The epidermal proliferation was clearcut and occurred consistently enough to be of significance. The response varied with (*a*) the age and sex of the patient, (*b*) the concentration of the estrogen in the ointment, (*c*) the method of application, (*d*) the duration of contact and (*e*) the total duration of treatment.

A. The young women who made up group 4 showed no epithelial response at all. In this group, the application method was used for sixty days in 2 cases and for thirty days in 2 other cases; the inunction method was used twice daily for thirty days in 1 case. All the members of the group exhibited a fully developed epidermis of normal

thickness and normal-appearing corium, as evidenced by a base line biopsy made before treatment. Therefore, no change in the skin within the normal histologic limits would be perceptible, and only an abnormal effect on the skin could be seen. Theoretically, no changes would be expected. Women of such an age group would normally secrete adequate amounts of their own estrogenic substances. It would thus appear that the local application of estrogens to the skin of such young persons would produce no changes; and, as expected, no changes were observed.

B. No definite changes were observed in the skin of the 5 men similarly treated (4 in group 1 B and 1 in group 2). However, 1 man (group 1 B) did exhibit a change of almost negligible degree after thirty days of treatment; this change persisted, without further progression, for the next thirty days, during which applications were continued. The degree of change was similar to that produced by the control (estrogen-free) ointment and may therefore have been adventitious. Theoretically, no change would ordinarily be expected in the male skin from the application of estrogen substances. (The results, however, may be somewhat different in degree if extremely high concentrations of estrogens are applied topically.)

C. In all the postmenopausal women (groups 1 A, 3 and 5), definite effects on the epithelium were observed histologically. All the changes were identical in kind and varied only in degree. Base line biopsies performed before treatment almost invariably revealed the picture of a senile, atrophic skin. Often the epidermis was only four to five cells thick. The basal layer in most instances showed small, cuboidal cells and the absence of epidermal pegs. In a majority of cases there were atrophic changes in the accessory structures, such as the hair follicles and sebaceous glands. The most pronounced atrophic changes were usually accompanied with a peculiar clumping and degeneration of the elastic fibrils.

Histologic changes began to appear at varying intervals after the use of inunctions or applications of the estrogenic ointments. In the majority of cases no effect occurred until after twenty to thirty days' use of the ointment, although in a few cases changes appeared at the end of ten days. Within thirty days a typical response had appeared in all but 2 cases. Since biopsies were made at about ten day intervals, an excellent opportunity presented itself of determining the time of appearance and the type of the change; thus, there appeared first an increase in the size of all the cells and a return to more normal staining qualities. The cytoplasm tended to increase in volume, at the same time staining less intensely; the nuclei, similarly, increased in size and assumed a rounded, rather than ovoid, form, with the chromatin network becoming more prominent. At the same time, the beginning waviness of the basal cell layer was evidence of proliferation of its cells.

In subsequent biopsies these changes became more pronounced; the epidermal cells approached their normal size and increased in number, so that the epidermis resumed its usual thickness and appearance. With the increased waviness of the basal cell layer, the normal-appearing pegs developed in the corium, the capillary blood supply became prominent and the supportive elastic fibrillar structures likewise became more pronounced. In a few cases no epithelial pegs were formed, but the increased size and number of the cells of the epidermis itself gave ample evidence of the typical picture of a proliferative change. Case A (fig. 1 *A*) illustrates the typical development of these epidermal changes in 1 of the postmenopausal women of group 1 A. This degree of change was the average observed with continuous application of the ointment with the weakest concentration. The maximum degree of change noted with this ointment is shown in figure 2 *B* and *C* (case B, group 1 A). This figure also illustrates the degree of the changes produced by the ointment base alone (fig. 2 *B*). Surrounding a sweat gland there is a moderate degree of infiltration with lymphocytes. This was a common feature, occurring in cases in which ointment was used, regardless of the presence or absence of estrogen.

Changes affecting the elastic tissue and collagen of the underlying corium were observed with any degree of certainty in only 5 cases of the entire series. Even in these 5 cases the changes were so minimal that they might easily have been overlooked had it not been that serial sections of biopsy material were available for study. On the other hand, it must be recognized that the small number of cases in which these changes in the elastic tissue were noted does not of necessity reflect a true state of affairs. The technical difficulties encountered in staining elastic fibrils, even with Weigert's method, are well known. This makes extremely uncertain even the qualitative evaluation of such changes in the elastic fibrillar structures; only when such changes were pronounced was it possible to estimate actual quantitative alterations in the character and distribution of these fibrils.

Figure 3 *A*, taken from 1 of the patients of the younger premenopausal age group, served as a control in estimating the elastic fibrillar network in the normal skin. By contrast, in a section showing the most extensive changes observed in the postmenopausal patients before treatment, there was a curious clumping of the elastic tissue fibrils in atrophic skin and a loss of the fine elastic network throughout the corium. In many cases there was a similar granular degeneration of the collagen in the immediate subepidermal zone and an increased density of the collagen in the deeper layers. This is shown rather characteristically in figure 3 *B*, which represents the average appearance of these postmenopausal degenerative changes. Figure 3 *C*, taken from the same patient as *B*, after sixty days of treatment with estrogenic

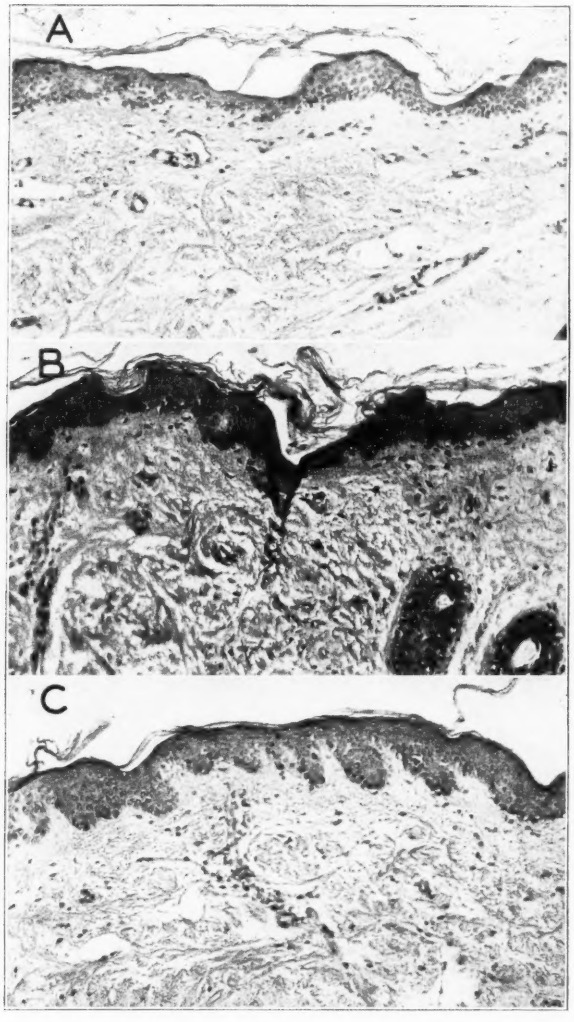

Fig. 1.—Average response of senile female skin to continuous application of ointment containing 242 international units of estrogen per gram (7,500 international units per ounce).

A, biopsy specimen of the skin of the back before treatment. Note the thin epidermis, the absence of pegs and the cuboidal cells of the basal cell layer.

B, biopsy specimen of the skin of the back after application of an estrogen-free ointment for thirty days. There are thickening of the epidermis, greater cellularity and slight waviness of the basal cell layer.

C, biopsy specimen after application of estrogenic ointment for thirty days. Note the increased sizes of the epidermal cells and the pronounced waviness of the basal cell layer, indicating proliferative activity.

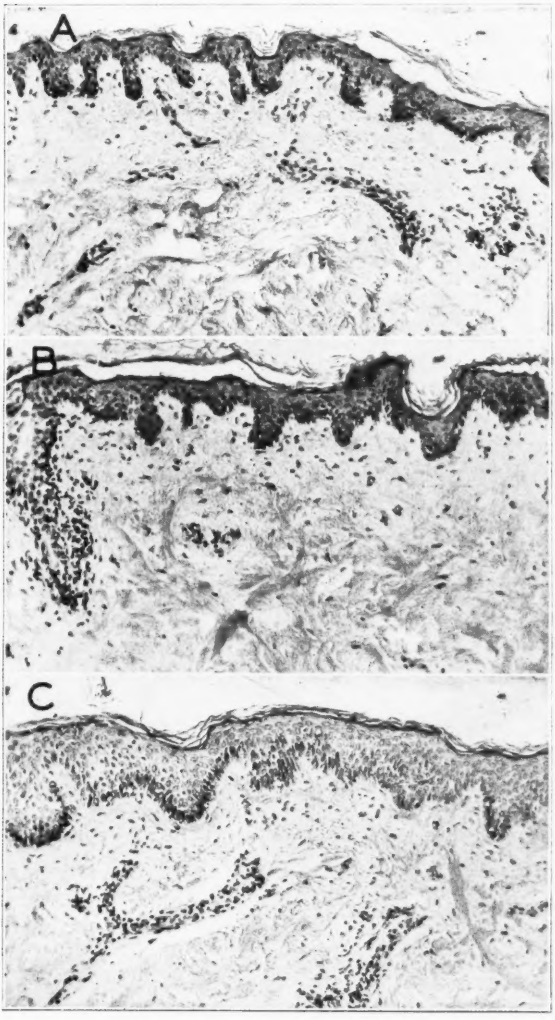

Fig. 2.—Maximum response of the senile female skin.

A, control biopsy specimen, taken before the beginning of treatment. The epidermis is thin; the pegs are also thin, though fairly numerous. There is slight pericapillary lymphocytic infiltration.

B, biopsy specimen after application of estrogen-free ointment for thirty days. There is slight, but definite, thickening of the epidermis, with chubby pegs and lymphocytic infiltration about a sebaceous gland.

C, biopsy specimen after application of ointment containing 242 international units of estrogen per gram. Note the definite regeneration and thickening of the epidermis. The cells themselves are large and vesicular; the keratin is fragmented. There is moderate pericapillary infiltration with lymphocytes. . This degree of change was observed consistently when 484 international units of estrogen per gram (15,000 international units per ounce) in white petrolatum was used.

substance by the application method, illustrates the extent of reversal of these changes encountered in the 5 cases cited. There are disappearance of the degenerated fibrils and beginning reappearance of the fine fibrillar network, and even the collagen shows a reversion to a more nearly normal fine, fibrillar, wavy architecture.

The changes in the epithelium of the skin tended to reach a maximum at sometime between thirty and fifty days. In general, this was attained more promptly with the larger doses and the more constant, prolonged period of contact of the estrogenic material. When this level was reached, no further progression was observed, although these changes appeared to be maintained as long as therapy was continued.

Our studies revealed that there was a latent period of ten to twenty days before demonstrable changes could be observed; this was followed by a relatively rapid response of the epithelium, which reached its maximum between thirty and fifty days and then leveled off.

The concentration of the estrogens also influenced the effects. The greatest and most consistent effects were observed in group 5, in which the ointment contained 15,000 international units per ounce. The twofold increase in concentration appeared to exert effects in a much shorter time than that for the lower concentration, namely, 7,500 units per ounce. The purpose of cross control was served here, since the patients in group 5, in whom these rapid effects were observed with the use of an estrogen ointment containing 15,000 units per ounce, were at first part of group 1, in which the estrogenic ointment containing 7,500 units per ounce was first used. The natural deduction here is that, despite the fact that petrolatum, which was the vehicle in the 15,000 unit preparation, is a poor substance in favoring absorption, the increase in estrogen concentration overcame the lack of absorbability on the part of the petrolatum.

The results clearly indicate that the duration of contact is an important factor: The method of continuous application (with glassine® paper) in group 1 A gave a response in 83.3 per cent of the cases, while the shorter inunction of the same material produced a response in only 71.4 per cent in group 2.

In group 3, in which ointment containing 15,000 international units per ounce was used, and in which a surprisingly low percentage of positive results was observed, an extraneous factor entered. The patients of this group were paralytic and incontinent. During the middle period of the experiment, a mild epidemic of diarrhea broke out in this group. This unfortunate combination of circumstances necessitated unusually frequent bathing of the patients; hence, the ointment had an extremely short period of contact. It is to be expected that had the conditions in group 2 and group 3 been similar the latter group (with the higher dosage) would have shown a higher proportion of positive results.

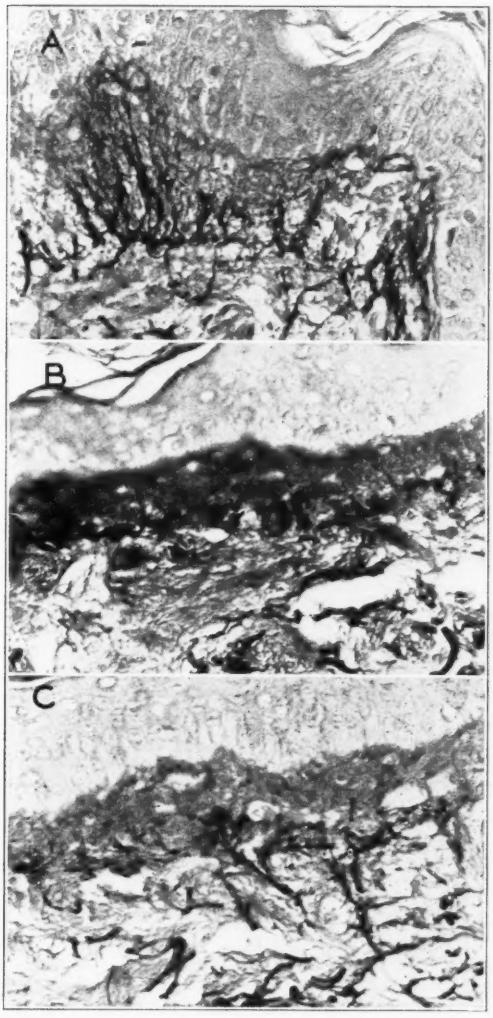

Fig. 3.—*A*, elastic fibrillar tissue of normal skin of a young woman. Note the sharp basal layer of fibers, from which fibrils radiate up into the pegs.

B, senile skin before treatment. Note the clumping of the basal plane of elastic fibrils and the disappearance of the radiating strands, as well as the scarcity of fibers in the deeper layers.

C, specimen from same patient as that represented by *B*, after treatment for sixty days with inunctions of 484 international units of estrogen per gram of ointment. Note disappearance of the clumping and beginning regeneration of fine fibrils. The deeper fibrils also appear to interweave in a more homogeneous pattern.

Since the question of the relation of malignant changes to sterols has been prominent in the literature, particular attention was paid to the cytologic character of the epidermal cells of the patients showing a response to estrogen. It can be stated unequivocally that no abnormalities were observed: There was no increase in the number of mitoses, or any suggestion of changes other than those of simple regeneration.

3. *Systemic Effects of Estrogen.*—It is well known that estrogens applied to the skin can be absorbed into the systemic circulation. From Zondek's work, it is known that about seven to ten times the dose given parenterally is required for an equal effect by percutaneous application. In effect, then, about one-seventh to one-tenth the percutaneously applied estrogen is utilized systemically. This would amount to a daily supply of 100 to 500 international units in group 1 A. That this exceedingly small quantity should produce any change whatever, even on the most sensitive systemic indicator of estrogenic activity (the vaginal epithelium), would be most surprising. This amount of estrogen is within the normal daily variation of the estrogen output of a normal menstrual woman. It is evident, however, that the changes in the vaginal smear were of minor degree and were totally absent in 4 of the 17 cases in which smears were examined. In only 1 case was the change of any significant degree, even with our method of grading. There were, of course, no mammary or other systemic estrogenic manifestations, since these tissues are less sensitive than the vaginal epithelium.

The vaginal smears showed that the estrogens absorbed from the ointments were of negligible effectiveness, even on the vaginal epithelium. It is not likely, therefore, that the absorbed estrogen should affect the cutaneous epithelium via the systemic route (in the concentrations under discussion). The photomicrograph in case D (fig. 4, *A* and *B*) bears out this assumption: The expected hyperplasia of the epidermis is shown in figure 4 *A* (case D), and the effects of the systemically absorbed estrogen on the vaginal smear (case D). The epidermis of the other (control) thigh, however, showed no estrogenic effects (fig. 4 *B*). The deduction that primarily the estrogen absorbed from the ointments acted locally, and not as the result of systemic absorption, is based on the observation that estrogenic changes as described were present even in those patients in whom a vaginal change was absent.

Dr. Lawrence W. Smith, formerly professor of pathology at Temple University, Philadelphia, reported the total histopathologic picture as follows:

There can be no question that this hormonal agent, when applied to the epithelium of patients in the postmenopausal group, showed striking changes,

with a reversion toward the normal picture. In the series of cases in which 15,000 units of estrogen was rubbed into the skin daily for three weeks or more, the biopsy specimen taken at the end of this period, as compared with the pretherapy (control) specimen, showed remarkable changes. With 7,500 units, these changes could likewise be demonstrated, but the results were roughly proportionate to the dose of 7,500 or 15,000 units.

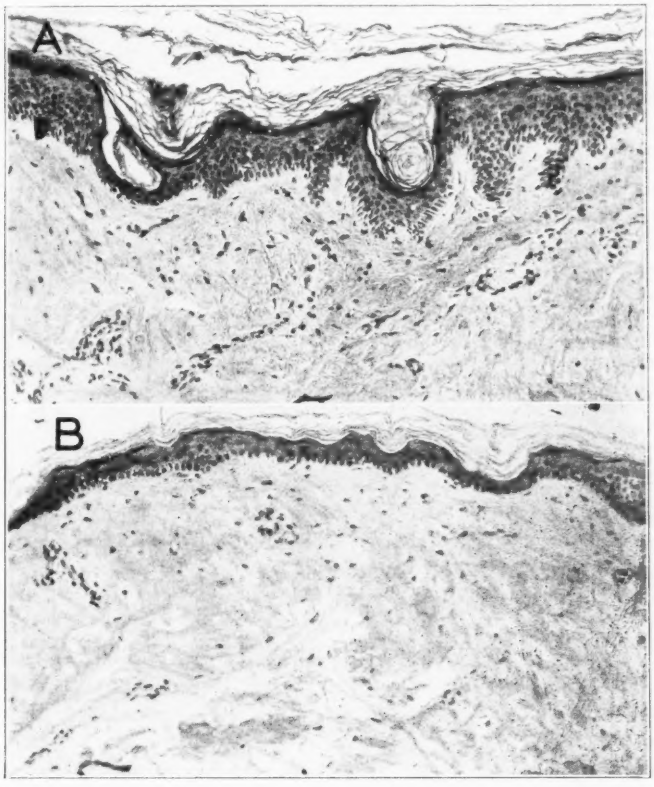

Fig. 4.—Absence of cutaneous effects of systemically absorbed estrogen. *A*, anterior surface of thigh after inunction of 484 international units of estrogen per gram. Regeneration and thickening of the epidermis have taken place. *B*, skin of opposite thigh after inunction with estrogen-free ointment only. There is no perceptible change, showing that neither estrogen-free ointment nor systemically absorbed estrogen has any cutaneous effect.

The original specimen in each instance showed characteristic senile atrophy with thinning of the epithelium, loss of rete pegs and a tendency of the nuclei of the cells to become small, compact and hyperchromic. After the experimental period, the epithelium regularly showed proliferative changes with thickening and the reformation of fairly normal-appearing rete pegs and nuclear changes, a change

which might be considered as representing essentially normal epithelium, as seen in the young (premenopausal) age group. Subsquent biopsy specimens obtained a week or ten days later, after omission of treatment during this period, again regularly showed a definite trend toward reversion to the previous atrophic picture. Reapplication of the hormonal material for a supplemental three week period again resulted in the same proliferative changes as those seen in the biopsies taken at this time.

It is of interest to note that similar studies carried out on epithelial tissues in young women in the 20 to 30 year age group (premenopausal) and in the male subjects showed no demonstrable histologic changes of the epithelial structures.

It is likewise of interest to note in certain cases in which vaginal smears were taken from the late postmenopausal, senile group that systemic effects of this topical application of hormonal material could be observed in the proliferative changes in the vaginal mucosa. However, biopsy specimens taken from areas of the skin other than those treated topically showed no microscopic changes which could be attributed to any systemic reaction from the topical therapy. This is, of course, not surprising, and indicates the high degree of selectivity of the epithelium of the reproductive tract in response to these hormonal influences.

Studies relating to the subcutaneous structures, particularly the elastic tissue of the corium, are much less definite. In a few instances, there appear to be a definite increase in the elastic fibers and a somewhat more normal distribution after therapy. However, these changes are so minimal and so irregular in their occurrence that I do not feel one is justified in making any statement regarding the effectiveness of such topical hormonal therapy on the elastic tissue of the corium.

It would be interesting to see whether such minimal changes as were observed in these few instances would be found regularly were therapy to be continued over a much longer period.

Dr. Fred D. Weidman, who also examined the slides, stated:

The controls appear to me to be as complete as is humanly possible in this type of investigation. The epidermal hyperplasia was clearcut, though not great by any means, but it occurred so consistently that it surely has significance.

The results have only a biologic interest, namely, that locally applied estrogen can induce a slight hyperplasia of epidermal cells.

A summary of the pathologic report follows:

1. The topical application of natural estrogens has a direct effect on the epidermis of postmenopausal women. No changes in the skin were found in young women with normal endocrinal function or in the men studied.

2. The effect on the epithelium was proportionate to the concentration of estrogen in the ointment and to the duration of contact. Concentrations of 242 and 484 international units per gram (7,500 and 15,000 international units per ounce) used by inunction regularly produced definite and consistent proliferation of the epithelium. These effects were first noted at some time between ten and thirty days, reached their maximum in thirty to fifty days and did not progress thereafter. The proliferative changes of the epidermis were evidenced by an increase in the number of cell layers and the reappearance of the epidermal pegs. The epithelial cells themselves showed an increase in

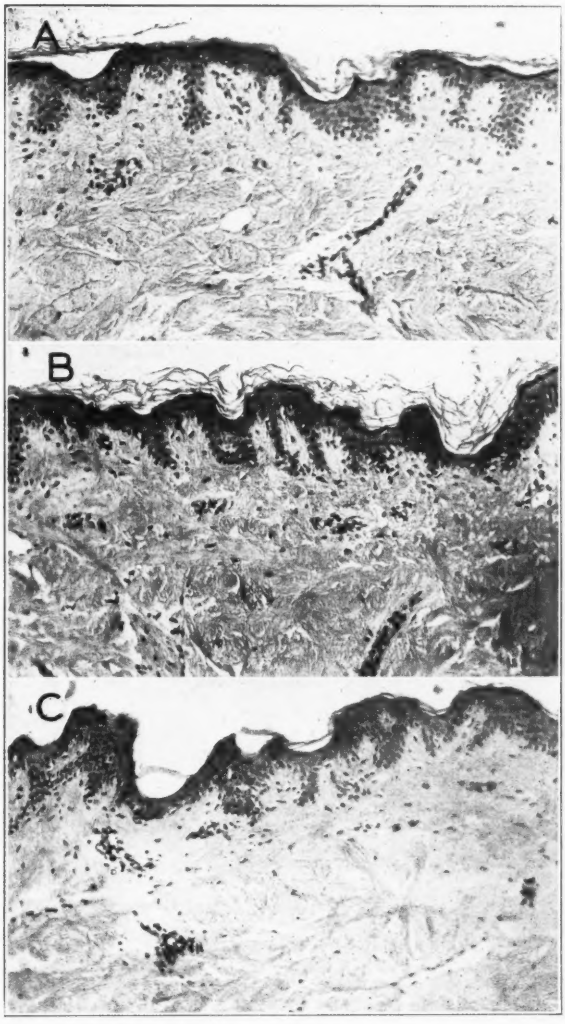

Fig. 5.—Absence of response in skin of a young woman.

A, biopsy specimen from the skin of the back before treatment. Note the essentially normal epidermis with large, well developed pegs and vesicular cells.

B, biopsy specimen taken after inunction of estrogen-free ointment for sixty days. There is no perceptible change.

C, biopsy specimen taken after inunction of ointment containing 242 international units of estrogen per gram. There is no difference between this and the control biopsy specimen.

size of both nuclei and cytoplasm. No anaplasia, mitosis or other abnormal change was noted.

3. Vaginal smears (from postmenopausal patients), used as an indicator of systemic absorption, showed no changes in 4 cases, barely perceptible changes in 12 cases and a definite, but minimal change in 1 case of a total of 17 cases in which smears were examined. Less sensitive tissues, e. g., the mammary glands, showed no changes.

4. The inunction of estrogen-free petrolatum produced no demonstrable histologic changes in the skin. The estrogen-free ointment induced minimal proliferative changes.

745 Fifth Avenue.

ABSTRACT OF DISCUSSION

DR. JOHN A. GAMMEL, Cleveland: The experiments of Eller and his associates deserve our compliments. They have gone into all desirable detail concerning experimental data, doses and time factors.

These experiments were carried out on an impressive number of patients, with an average of nine biopsies per patient. The presenters must have applied unusual persuasion to secure such a number. Their conservative interpretations are reassuring and are based on sufficient material, with proper checks.

These experiments are of practical value to us as dermatologists, as we are frequently consulted by our patients concerning the merits or dangers of estrogenic creams which cosmetic manufacturers recommend as restorers of a youthful complexion. We must know what can be expected from the application of such creams. I have used an estrogenic cream with a potency of 7,500 units per ounce on various occasions and found that the patients liked it and believed that their skin felt fresher and more elastic.

I am particularly interested in the pilosebaceous apparatus and the sudoriferous glands, because Dr. H. J. Ropshaw, of the Institute of Pathology of Western Reserve University, and I are engaged in experiments concerned with the autonomic innervation of the skin and its action on the glands. As the function of the sebaceous glands also seems closely related to the presence of sex hormones, I am surprised that no response in these appendixes of the skin was seen in the authors' experiments.

Biologically, there is another approach, namely, that of keratinization. Besides other functions of the skin the production of keratin is the most important, rendering the skin the protective organ that it is. There is a constant chemical action going on in the various layers of the skin. Some dermatoses appear during the menopausal period.

By establishing and defining the dermoestrogenic syndrome, we could bring a few clinical problems nearer to solution. Dr. John H. Lamb's paper, yesterday, was a step in this direction.

The histologic picture presented by Eller and his associates differs somewhat from the observations of Sharlit, who, before the Louisiana State Board of Health last year, emphasized the hydration of the collagen and the dilatation of the capillaries after the use of estrogenic creams over a period of six months.

Sharlit expressed the belief that the hydration of the collagen increases the mass of the derma, which, in turn, stretches the overlying epidermis and mechanically obliterated wrinkles. At the same hearing, Traub stated that the elastic

fibrils multiplied in 60 per cent of his cases, whereas Eller observed beneficial changes in only 10 per cent and described them as minimal.

Reynolds (*J. Invest. Dermat.* **4**:7, 1941), in his experiments on rabbits, noted dilatation of the capillaries and venules after parenteral administration of estrogens, and this reaction was seen even after denervation. In man, the dilatation started within three to fifteen minutes after the injection. It lasted forty-five minutes and was often still present at the end of two hours.

The apparent contradictions in the reports by Reynolds, the authors and Sharlit are due possibly to the time factor and the dosage. Reynolds described an immediate response of the minute blood vessels and a subsequent refractory period. After an hour or two the vasodilatatory action had subsided.

Eller observed a period of latency of many days, after which the estrogenic effect became evident in the epithelium. This is probably not the result of a better blood supply, for Reynolds showed that the rate of blood flow does not materially increase after the administration of estrogens.

I am well aware that there are biologic differences between the epithelium and the endothelium, but, inasmuch as the vessels respond even after denervation, the action is in both cases directly on the cells, which act as chemoreceptors. During the first two months of estrogenic medication, little, if any, dilatation of the capillaries is demonstrable at biopsy. At the end of six months, however, the capillaries remain dilated, along with other changes reported by Sharlit, Traub, Goldzieher and others.

The time factor needs further investigation, and it would be highly desirable to study biopsy specimens of the skin from the faces of patients who have used estrogenic creams for several years.

Dr. Marion B. Sulzberger, New York: This paper is of great theoretic and practical importance. No dermatologist meets a more baffling and difficult question than the one often posed by women who want to look younger, i.e., whether or not they should be permitted or urged to use the estrogenic creams which are now available and widely sold.

Until now, I have been unable to answer that question to my own satisfaction, for I believe there is no evidence that such creams do any actual good, and it is suspected that they may do a good deal of harm in some cases.

In view of the present report, how shall dermatologists now answer the women in quest of lasting youth? I am inclined to be even more careful than before with my advice, for if these studies, so well presented, demonstrate anything, it is that the estrogenic creams do have a definite local effect. If they have a specific biologic effect in one direction, it is possible that they may have a biologic effect in other directions.

It is known that in laboratory animals estrogenic substances used in adequate quantities have a carcinogenic action. The question, then, is: What is the safe quantity for the particular site, time interval and person? It is often said that the doses of these creams administered by local applications are so minimal as to be safe; this is not the case if one computes the local dose per cell. If there is any substantial penetration, the estrogen will get to the epithelial cells and cutaneous structures in many, many times the amount which arrives at those same cells and structures with each systemic administration for therapeutic purposes. One must consider that the dose may be a high local one and that the safe quantity which will have no carcinogenic effect in a particular patient, at a particular site, at a particular time, is not as yet known.

It will take many years to find out just what is or is not safe with regard to local applications of estrogens. In the first place, there is the question of indi-

vidual susceptibility; then there is the question of local readiness or resistance. Certain persons or areas may be susceptible and inclined to the development of cancer, while others are not. How can one be certain that a woman using a cosmetic containing a steroid hormone is going to stop short of the quantity which may produce a premalignant change or accelerate a malignant process? It might be wise to know the answer to this question before prescribing hormone-containing creams for purely cosmetic purposes.

Perhaps one can achieve equivalent cosmetic results with substances that are surely free from suspicion of having any carcinogenic potentialities. If, as some suppose, the hormonal effect is based mainly on vasodilating stimuli, one might be able to achieve equivalent effects with less suspicious substances, such as histamine-containing ointments in small doses or other local vasodilators. I should like to see Dr. Eller and his associates try such control applications.

I was astonished to hear Dr. Eller and his collaborators report that the senile skin of the male subject does not respond to applications of estrogens with increased growth of the cutaneous structures, whereas the senile skin of the woman does. It is hard to understand why there is this difference. I think that further research on this point is also required.

Dr. Fred D. Weidman, Philadelphia: I have been quoted in this paper, and I report at once that the specimens were submitted to me without my knowing "which was which." In other words, I went into the situation quite unbiased, nor did I know that my work was going to enter into the authors' presentation. I do remember that I wrestled with the matter of elastic tissue and that I could not satisfy myself that there was any change in this structure in any of the sections.

At that time, I did not know that the question of elastic tissue would enter into the thesis; I should like to point out that elastic tissue is not generally accepted as the factor responsible for the gross elasticity of the skin. Rather, it is the consensus that it is not the elasticity in tissue substance, but the pattern, that is, the network that gives the elasticity to the skin—just as a fish net, which is made of relatively rigid individual cords saturated with resinous substance, will as a whole have an elastic quality, so, in the skin, it is this network of collagenous, as well as elastic, tissue that is responsible for the elasticity. Therefore, in relating the amount of elasticity in the tissues of the skin to the gross elasticity of the skin, one should consider the arrangement of the collagenous tissues.

The authors have presented a morphologic study, but morphologic similarities do not always connote a biologic relationship. For example, in a case of ordinary contact dermatitis, there is multiplication of the epidermal cells as the result of an attempt at regeneration as a correction of surface damage. It does not necessarily connote a change in the general metabolism of these surface cells.

It is hazardous to evaluate conditions morphologically in the sebaceous and sweat glands. It is remarkable to see how little change they show, even when there is pronounced suppuration in the deeper parts of the skin. As a result, one learns indeed little as a guide to the diagnosis from conditions in the sweat and sebaceous glands. When it comes to evaluation of the size of these structures, one again runs into difficulties, knowing how the size of both these sets of glands varies in different parts of the body.

Dr. Joseph J. Eller, New York: With regard to Dr. Sulzberger's remarks, I have not seen any tendency toward carcinomatous growth in any of the treated areas.

With reference to Dr. Weidman's discussion, we were much more impressed with the changes in the epidermis than with those in the elastic tissue.

MEASUREMENT OF THE SKIN

President's Address

J. GARDNER HOPKINS, M.D.
NEW YORK

IT WAS, I believe, Descartes who said, "Science is measurement"—a statement certainly open to question. However, the importance of measurement to science is generally recognized. It is tempting to express it as an equation in simple arithmetic: "The difference between science and guesswork is measurement," from which statement one would derive the conclusion, "Science minus measurement equals guesswork."

Now I would not disparage guesswork based on observation. Informed guesswork pays off at the race track. It has often won battles and in our field has saved many lives, but it can get one into serious trouble. Its pursuit is nerve-racking and provocative of gastric ulcers. It is a great comfort to the mind to deal with things that can be measured.

When I first entered medical school my eye was caught by a phrase in the announcement of the university. We were to be instructed in many, many things, among them "the use of instruments of precision." As a bewildered student on the wards, I often wondered what these instruments of precision were. I could identify only the clinical thermometer, some blood-counting gadgets and a blood pressure machine.

Since then medicine has come a long way. We physicians think of diabetes almost entirely in terms of measurement. We diagnose diseases of the heart and of the peripheral vascular system by measurement. Treatment of shock is controlled by measurement of blood proteins and electrolytes. In nephritis we measure what the glomerulus is doing and what the tubules are doing. We have some, not particularly satisfactory, methods of estimating what goes on in the liver. What means have we for measurement of the skin ?

The various cutaneous tests by which we assay immunity and allergy are almost the only measurements frequently employed in diagnosis. Despite their lack of sharp end points and the difficulty of true quantitation, they are dependable because of the firm principles underlying them. We have other procedures, among them Nomland's test for amyloid and Senear and Caro's for histiocytes. We use many indirect methods, such as measuring the blood or the urine, but too often we merely look and

Read at the Sixty-Eighth Annual Meeting of the American Dermatological Association, Inc., San Diego, Calif., April 26, 1948.

draw conclusions. You will recall that when Jadassohn introduced what is now known as patch testing he called it "functional testing of the skin." This phrase indicated his hope that by further functional testing far more might be learned. Why the prevailing lack of methods?

For one thing, it is a difficult business, this measurement of the skin. Any bit of skin contains connective tissue, blood vessels, nerves, one or two kinds of glands and many types of cells. Each cell itself contains a nucleus, mitochondria and other particles and a host of distinct enzymes. When we measure skin we often find it hard to tell which of these elements determines the result.

Such problems beset the measurement of most organs, but the skin presents its own peculiar difficulties. Various areas differ in their makeup and in their activities. What we find out about the scalp may not be true of the palm. The glands have no common duct, and we cannot readily collect their secretions. Moreover, the skin is often contaminated by foreign chemicals and visiting microbes, whose presence is purely accidental. Its temperature and other conditions vary with changes in its surroundings. Briefly, the skin as a mass is not homogeneous; its topographic divisions are not homologous, and samples are difficult to obtain in a pure state. These facts confuse measurement.

Probably it is not so much these difficulties as the accessibility, the ease of inspection of the skin, that has delayed development of measurement. Many diagnoses can be securely made by inspection, and the dermatologist has not felt the same need of "tests" as has the internist, who cannot see what he is about. A friendly scientist put it to me in this way: "Skin disease attracts the naturalist, the enjoyer of phenomena as such; and in his enjoyment he often sees no need to apply severely critical methods. It is as if he were watching the birds or the flowers."

Be that as it may, we all feel every day the need of greater certainty in diagnosis. I do not undervalue careful observation, which must form the foundation of any sound diagnosis, but opinions based on inspection of the patient or of a section of his skin suffer from the chances of error inherent in any personal judgment, the element of "guesswork." In case of doubt or of difference in opinion we have few exact methods for determining the truth.

If measurement is needed in diagnosis, it is far more needed in research. It may emphasize this to recall the story of the development of BAL (2,3-dimercaptopropanol) by Peters and his associates. You will remember that in studying the action of arsenical blister gases Thompson found that they inhibited the cutaneous enzymes responsible for pyruvate oxidation. Stocken and Thompson discovered that, among many sulfhydryl compounds tested, BAL not only prevented inhibition

of a pyruvate oxidase system by an arsenical but also reactivated the enzyme after inhibition. This compound, when applied as late as one hour after exposure, prevented blistering from lewisite (β-chlorovinyldichloroarsine). By precise measurements these investigators discovered not only a means of protection against this weapon of warfare, which, fortunately, was never used, but an agent that proved astonishingly effective in the all too frequent lesions caused by the arsphenamine compounds and by compounds of mercury and gold.

To illustrate a matter I shall speak of in a moment, I would remind you that the technics and the whole line of thought employed by Peters' group were based on the work of many previous investigators, who probably had no practical applications of their results in view. Certainly, whatever the purpose of the pioneer work on respiratory enzymes by Warburg in the Kaiser Wilhelm Institute, it was not to protect British soldiers from gas attacks by the Reichswehr.

Although the skin presents difficulties to measurement, it offers also peculiar advantages. Chief of these is its accessibility, which permits testing without disturbance of its natural relations. One can take samples of it at will. Methods developed by Baumberger and Medawar permit clean separation of epidermis from cutis. It is thus the only tissue except the blood of which the cells, freed of their supporting fibrous structures, may be obtained for study and analysis. This fact should aid in the solution of problems difficult to attack in other organs.

A large and valuable reservoir of data as to the skin has already been accumulated. Recently MacKenna has written a book, "Modern Trends in Dermatology," [1] which has pages packed with figures and references. Men have cannulated a capillary to determine its pressure or have picked up droplets from a single pore to secure uncontaminated sweat or have collected the hair from a thousand heads to obtain sufficient sebum for analysis. By ingenuity and diligence they have overcome difficulties imposed by the baffling structure of the skin.

This is not the place to catalogue this information. Much of it is scattered as to subject and incomplete as to any one substance or process. Much has not yet been correlated with the problem of origin and development of cutaneous diseases, doing so being a most difficult task. We have, however, these facts at our disposal and the means of establishing far more.

In spite of all that has been done, we are still unable to explain things we observe every day, such as edema and vesiculation of the epidermis and the astonishing phenomenon of the formation and reabsorption of bullae, or, in exfoliative dermatitis, the continuous desquamation of a

1. MacKenna, S.: Modern Trends in Dermatology, New York, Paul B. Hoeber, Inc., 1948.

keratin layer that seems to be rapidly and efficiently formed. We know well the atrophic, the hyperkeratotic and the pigmentary and vascular changes produced by radiation but have little information as to how they are produced. The observations of Epstein and Grünmandel have indicated that local immunity probably explains the annular form of ringworm and impetigo, but we see little significance in the characteristic pattern of erythema multiforme or of many circinate and serpiginous lesions. The peculiar distribution on which we base our diagnosis of many eruptions is quite mysterious. We need far more information to understand the pathogenesis of most dermatoses.

To obtain this information we need research, but what kind of research? And what is research, anyway?

The person who asks 500 men what kind of shaving soap they prefer or what their sexual behavior has been thinks he is doing research. So does the young woman who designs the correct hat for a character in a cloak and sword movie—or her sister sent out by a department store to find out what its competitors are charging for spring underwear. And —may the Lord help us and save us—the young doctor who plasters a new antiperspirant on 100 backs and reports irritation on 10 per cent of them thinks he is doing research.

How shabby words become with use. Some actually seem to decay. The name research, so inspiring years ago, has of late developed such a bad odor that some have tried to substitute the word investigation. They found, however, that to many persons an investigator meant a person called in to find out what had happened to Mrs. Smith's jewels or to trail Mrs. Jones's husband on his evening divagations. So we still say "research," and shudder when we say it. Perhaps the procedures just mentioned are research, but what is needed to bring clearness to dermatology is research of quite a different order.

We are all impressed by the achievements of science during the war, but I suspect that the triumphs of the Office of Scientific Research and Development were due more to development than to research. A great reservoir of knowledge accumulated during years of peace was tapped to solve problems forced on us by that emergency. I would recall again that the brilliant studies which resulted in the development of BAL were made possible only by preceding investigations of cellular enzymes made with no such end in view. It has been wisely said that there was a net loss in real scientific advance during the war because the efforts of investigators engaged in basic research were diverted to the solution of practical problems.

Progress in methods of measurement and in basic information as to the chemistry and physiology of the skin will come largely from studies of chemists and physiologists. Much can best be done in basic science laboratories unhampered by clinical control. Other aspects of our

problems can be grasped only by those with clinical training in dermatology. We need, besides purely laboratory men, clinical investigators who, as Zinsser expressed it, may serve as a bridge over which the discoveries of the laboratory may come to our aid in treatment and diagnosis. To serve thus investigators must be well grounded both in the clinic and in the laboratory. We may be able to recruit men already experienced in the laboratory and give them training in the dermatologic clinic, or we may send certain young clinicians into the laboratory for training. The efforts of these clinical investigators should, like those of their co-workers in the laboratory, be directed toward enlarging our understanding of disease rather than specifically toward development of diagnostic and therapeutic procedures. These will come swiftly as knowledge increases. They will be the invisible by-products of knowledge, as was the development of BAL. Alan Gregg has summed up this idea in one sentence: "Research is the response to curiosity, not to need."

We talk much of the lack of wards and laboratories, of supplies and technical assistants and of adequate salaries for investigators. These are but accessories. Men with original ideas and sound training are our true need. These men must have means to live and facilities with which to work. In fact, if we expect able young men to devote themselves to dermatologic research, it would be well that professorships at substantial salaries be provided to which they might hope to progress. Admittedly, such provision would require large funds.

However, I am reminded of a rumor, probably quite apocryphal, which my fellow medical students and I firmly believed. It was that our professor of anatomy had declined a call to an older institution, not because he objected to the larger salary offered but because he thought the laboratories were too elaborate and too full of apparatus. He feared that all that might distract him from his work.

The popular belief that all one needs to find a cure for cancer or to prevent infantile paralysis is a lot of money is reflected in the apparent confidence of Congress that a large enough appropriation will solve any problem. It is the great American fallacy of the moment. Actually, money is of no use until it is well spent.

You may differ violently with what I have said about the value of buildings, money and equipment because you have long been handicapped by the meager facilities now granted dermatology in universities and hospitals. Even so, I hope you will agree at least that the investigator is more important than the tools with which he works.

If these things be true, how can we best push forward the science of dermatology? We cannot all be Duhrings and endow laboratories for dermatologic research. Few can hope even to raise funds for such a

purpose. We should, however, be able to do what is more important—attract investigators to our field and encourage them in their work.

How can we interest the right men? We cannot do it simply by offering good salaries. In some way we must let them see the interest and importance of the problems of dermatology. In some cases experiences in the war did that task for us, but why has it been so difficult in general? The failure of young men entering clinical investigation to see the attractiveness of dermatology as a field makes one question their acuity of observation. Perhaps we could entice them while they are medical students if we talked more of function and less of morphology, if we showed them cutaneous lesions as enthralling phenomena, not just as things to be made to vanish.

Once a man is attracted to dermatology as a field of endeavor, we can do much to assist him. What I wish to say on that point involves another digression.

At the present day the curriculum of most medical schools is packed and rigid. Medicine is a complex subject. A dozen departments pour information into the students until they fairly bulge. They have little incentive, and practically no time, to observe and think for themselves. Most become what my scientist friend calls "mere acceptors of the didactic word." Possibly this procedure is necessary in equipping doctors to meet the myriad problems of general practice, but it does not seem much like education, and certainly does not excite an appetite for research.

Training graduates in dermatology as their specialty is another matter. It would seem that here we might escape the necessity for cramming methods. In his presidential address last year, Paul O'Leary stated well the case for freedom in graduate study, for a liberal and elastic program of training. There is no great mass of factual material essential to memorize. I wish there were more. What the student needs is time. Yet there is a tendency to make his course harder by the erection of all sorts of artificial bunkers and hazards. I hope it will not seem disloyal to a group with whom I have been much honored to serve if I say that in this respect the American Board of Dermatology has had an evil influence. Its examinations necessitate cramming, and this necessity discourages individual effort to look into the unknown. Personally, I have been pleased when some of my students have failed in the Board's examinations because, knowing their very real abilities, I have felt that their failures indicated that they had been more interested in studying cases than in memorizing books. In this connection, the recent comments of Dean Chesney on the specialty boards should provoke thought. He suggested, among other things, that the requirement of work in the basic sciences be no longer a requirement, only a suggestion.

All this discussion leads on to the question of what we can do if by good fortune we find a man who does not totter mentally when released from the plaster cast of the medical school in which he has been encased for four years, a man who actually can still observe and think for himself. We should and we can do much to help him on. We can give him freedom to study what interests him most and aid toward the training his investigation may require. We can encourage him by interest in his ideas, even if they seem a bit on the underdone side. We can even learn to bear his condescension toward our most cherished beliefs. With good luck, we may eventually be able to find him a post where he can continue his investigations and teach when his apprenticeship is ended.

I hope the foregoing statements have not seemed like a pretentious way of saying something simple and obvious. I believe there is a principle involved. Measurement is not the only way to a useful decision, but it does give to any decision firmness and reliability. It will be long before a cutaneous disease can be expressed by a mathematical equation, but we should all like to go beyond the stage of the birds and the flowers. If we are to escape from empiricism and the errors to which it leads, one way is by measurement. It would promote our understanding of the diseases in our field and the skill with which we manage them if we made exact measurements of what we see and developed quantitative concepts of what goes on.

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RELATION OF EXIT DOSE AND OTHER DOSAGE FACTORS TO ROENTGEN INJURIES

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IN DECEMBER 1944, Andrews, Braestrup and Heisel [1] published a study of the exit dose in dermatologic roentgen therapy. This factor was defined as the amount of radiation received by the skin opposite an irradiated surface. Their work suggested that the exit dose was an important reason for the localization of radiodermatitis on the middle part of the face, hands and feet following low voltage roentgen therapy. Since this paper was presented chiefly from an experimental point of view, the purpose of the present study is to show the clinical significance of the exit dose. Tables are included which set forth the exit dose values at various kilovoltages commonly used in the treatment of simple inflammatory dermatoses. It is in these diseases that fractional dosage is repeated on extensive areas. When this radiation is used on the face and extremities the exit dose becomes an important consideration.

Numerous reviews of roentgen injuries have appeared in the literature since 1902 when Codman [2] reported a series of 167 cases of accidental roentgen ray injuries. Among these are studies by Hazen,[3]

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1. Andrews, G. C.; Braestrup, C. B., and Heisel, E. B.: Exit Dose in Dermatologic Roentgen Therapy, Arch. Dermat. & Syph. **50**:355 (Dec.) 1944.

2. Codman, E. A.: A Study of the Cases of Accidental X-Ray Burns Hitherto Recorded, Philadelphia M. J. **9**:438, 1902.

3. Hazen, H. H.: The Cause and Prevention of Radiodermatitis, J. A. M. A. **97**:1881 (Dec. 19) 1931.

Saunders and Montgomery,[4] Witwer and Leucutia,[5] Leddy and Rigos,[6] Curtis [7] and Uhlmann.[8] All of this material is necessarily so incomplete that it is difficult to associate the quality and dose of radiation used with the sites of injury. A similar problem has been encountered in this present study.

In an attempt to correlate the sites of occurrence of radiodermatitis with the exit dose, the records of 160 patients with late roentgen injuries were reviewed. Since 1932, 111 of these cases were available from the Columbia Presbyterian Medical Center and 49 from private dermatologic practice.

The incidence of radiodermatitis following both high and low voltage radiation is difficult to estimate. According to data from both the hospital and the outpatient services at the Medical Center, radiodermatitis was diagnosed in approximately 1 patient in 7,000 during this fifteen year period.

On the other hand, in a private dermatologic practice during a five year period (1942-1946) 33 patients among 9,600 new patients had radiodermatitis or 1 in 290, about 0.3 per cent. This incidence approximates the figure reported from the Cleveland Clinic of 1942.[9]

Of these 160 cases, the condition occurred in 39 (24.3 per cent) after roentgen ray therapy for nondermatologic conditions, such as carcinomas of internal origin. Twenty other patients (12.5 per cent) were observed with injuries following exposure to roentgen rays either for diagnostic purposes, such as fluoroscopy, or as a result of occupation (physicians, physicists, dentists, technicians and veterinarians). Sixteen others (10 per cent) had late changes following treatment for hypertrichosis either by "Tricho Institutes" or by physicians.

A more detailed analysis was made of the remaining 85 cases (53 per cent). These patients had been treated with roentgen rays for dermatoses, in some of which this therapy has already been greatly modified or has been abandoned. Of this group, 38 were men and 47 were women. The ages ranged from 6 to 66 years. All patients who received radium or roentgen irradiation for cutaneous epitheliomas were excluded

4. Saunders, T. S., and Montgomery, H.: Chronic Roentgen and Radium Dermatitis, J. A. M. A. **110**:23 (Jan. 1) 1938.

5. Witwer, E. R., and Leucutia, T.: Late Sequellae of Divergent Biologic Skin Effects Produced by Roentgen Radiation with Varying Voltages, Radiology **34**:24 (Jan.) 1940.

6. Leddy, E. T., and Rigos, F. J.: Radiodermatitis Among Physicians, Am. J. Roentgenol. **45**:696 (May) 1941.

7. Curtis, G. H.: Radiodermatitis: Its Prevention as Sequel to Roentgen Therapy for Certain Common Dermatoses, Cleveland Clin. Quart. **9**:3 (Jan.) 1942.

8. Ulhmann, E.: Significance and Management of Radiation Injuries, Radiology **38**:445 (April) 1942.

9. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, New York, Paul B. Hoeber, Inc., 1937.

from this study. An attempt was made to secure accurate data relating to the quantity and quality of the radiation used in therapy as well as the technic of administration, but, because of the time elapsing since treatment, this was possible only in rare instances. It was difficult also to determine the time of the onset of radiodermatitis, since the majority of patients were not observed until years after therapy had been completed. Treatments had been carried out not only by dermatologists but by roentgenologists and general practitioners as well.

TABLE 1.—*Data in 29 Cases of Radiodermatitis*

Number of Patients*	Dermatoses Treated with Roentgen Rays	Sex		Location of Radiodermatitis				
		Male	Female	Face	Scalp	Neck	Trunk	Feet
1	Furuncle	..	1	..	..	..	1	..
9	Hemangioma	4	5	8	1	..	..	..
4	Keloid	1	3	..	..	1	3	..
1	Leukoplakia	1	..	1	..	..	..	..
1	Lupus erythematosus	..	1	1	..	..	..	..
2	Lupus vulgaris	..	2	2	..	..	..	..
1	Nevus	..	1	1	..	..	..	..
2	Tinea capitis	..	2	..	2	..	..	..
5	Verruca plantaris	3	2	..	..	..	..	5
3	Undiagnosed dermatoses	3	..	1	..	1	1	..
Total 29	.....	12	17	14	3	2	5	5

* Twenty-nine patients (group 1) with radiodermatitis on localized sites and unrelated to the exit dose of roentgen rays.

TABLE 2.—*Data on 56 Patients with Radiodermatitis*

Number of Patients*	Dermatoses Treated with Roentgen Ray	Sex		Location of Radiodermatitis					
		Male	Female	Face	Arms	Hands	Legs	Feet	Other
25	Acne or rosacea	5	20	25	..	..	..	..	.....
5	Allergic eczema	..	5	2	2	..	..	..	Neck—1
2	Dermatitis, chronic	2	..	..	..	..	2	..	Nipples—1
3	Dermatophytosis	3	..	..	..	..	..	3	.....
7	Hand eruptions	5	2	..	..	7	..	..	.....
1	Onychomycosis	..	1	..	..	..	..	..	Nails—1
3	Psoriasis	2	1	..	2	..	2	..	Trunk—1
2	Pruritus vulvae	..	2	..	..	..	..	..	Vulva—2
8	Sycosis vulgaris	8	..	8	..	..	..	..	.....
Total 56	.....	25	31	35	4	7	4	3	6

* Fifty-six patients (group 2) with radiodermatitis following roentgen therapy for superficial dermatoses. In cases such as these, the exit dose of roentgen rays may be related to the roentgen injury. Several patients had multiple areas of involvement.

Investigation of these 85 patients revealed that 29 (group 1) received roentgen rays or radium on relatively localized sites for dermatoses in which treatment is usually intensive (verruca) or for which there is a definite regimen of therapy (tinea capitis). Among these persons it was felt that the exit dose bore no relationship to the development of radiodermatitis because of the manner in which radiation was used.

The observations on these 29 patients are summarized in table 1.

The remaining 56 patients (group 2) were treated for dermatoses in which it is customary to give unfiltered or lightly filtered low voltage therapy in subfractional or fractional dosage.

Table 2 shows the diagnoses as well as the sites of injury in these cases.

The following discussion is limited to the 56 patients in group 2. It should be noted that radiodermatitis was present on the face in 35, on the extremities in 17 and on other sites in the remaining 6. Roentgen injuries in this small series therefore tended to appear more frequently on areas in which the exit dose is known to be high and where treatment is frequently administered to both surfaces of an affected part. In this particular group it was impossible to show that the exit dose was a factor in the production of radiodermatitis because of the difficulty in obtaining information regarding the amount and quality of radiation used. We wish only to emphasize the frequency with which radiation damage appeared on the face and extremities. Neglect in considering the exit dose when treating these areas by fractional exposures may be one of the reasons for the localization of roentgen injuries on these sites.

Of special interest were the late changes on the face in this group following radiation for acne or rosacea, allergic eczema and sycosis vulgaris. At the present time the use of roentgen rays in these dermatoses has been modified. Treatment of sycosis vulgaris by epilation is now outmoded, and sulfonamide antibiotic drugs have greatly reduced the need for roentgen rays in both acne and sycosis vulgaris.

In regard to the dosage of the roentgen rays administered to these patients in group 2, history revealed that the great majority received repeated exposures to the face over prolonged periods of time. From only 3 patients had a history been elicited of relatively few treatments: 2 women had received as few as six or eight, while 1 man described erythema after approximately five exposures, following which therapy had been discontinued by his physician.

In the majority of these persons, the onset of the radiodermatitis was insidious and tended chiefly to affect the middle part of the face with the nose, lips and chin showing the most decided changes. The development of chronic radiodermatitis on the middle part of the face, however, should not be considered as due solely to the high exit dose produced by treatment of the sides of the face. Overlapping of the fields and the possibility of a midface exposure technic must be regarded as additional factors in the development of roentgen injuries on the nose and chin. In this series excessive radiation was also an important associated reason.

INCIDENCE OF EPITHELIOMA

Statistics regarding the incidence of epithelioma in chronic radiodermatitis usually indicate only the number of patients in a series with malignant changes. Of more importance is the percentage of

patients with neoplasms, when the quality, amount and technic of the administration of radiation are considered. Information regarding these details is difficult to obtain.

In the literature the percentages of epitheliomas occurring in radiodermatitis have varied from 5 to 33 per cent.[10] Saunders and Montgomery [4] reported that epitheliomas developed in 10 per cent of all cutaneous roentgen injuries; this figure was increased to 19 per cent when only changes of the second and third degrees were considered. The over-all incidence of epithelioma among these 85 patients in groups 1 and 2 was 32.9 per cent.

In group 1 epitheliomas developed in 3 of 29 cases (10.3 per cent). On histologic examination these tumors were either of the basal squamous or of the squamous type.

TABLE 3.—*Incidence of Epithelioma*

Number of Patients*	Dermatoses Treated with Roentgen Rays	Patients with Epithelioma	Location of Epithelioma
25	Acne or rosacea	13	Face
5	Allergic eczma	2	Face
2	Dermatitis, chronic	1	Ankle
3	Dermatophytosis	0	.....
7	Hand eruptions	1	Dorsum of hand
1	Onychomycosis	0	.....
3	Psoriasis	2	Arm, leg, trunk
2	Pruritus vulvae	1	Vulva
8	Sycosis vulgaris	5	Face
Total 56	.....	25	

* Twenty-five patients in group 2 in whom epitheliomas developed in radiodermatitis.

In group 2 epitheliomas were present in 25 of 56 patients (44.6 per cent), as is shown in table 3. In several of these patients lesions of various histologic types developed on multiple sites.

Epitheliomas occurred on sites other than the face in only 5 patients; 3 were men and 2 were women. Histologic examination revealed squamous cell tumors in these persons.

The high incidence of radiodermatitis on the face was associated with a high incidence of epithelioma. Twenty of the 35 patients with roentgen injuries on the face had epitheliomas; 6 were men and 14 were women. Fifty per cent of these 20 persons had malignant lesions before the age of 40. In most instances the neoplasms occurred on the middle part of the face, chiefly on or about the nose and chin.

Biopsies of tumors were obtained in 16 of these 20 persons, and it is of interest that in 11 single or multiple basal cell epitheliomas occurred either as the only microscopic observation of neoplasm or in association with other lesions of the squamous cell type. The

10. Leddy and Rigos.[6] MacKee and Cipollaro.[9]

histologic observations are summarized briefly: 3 squamous cell epitheliomas, 2 basal squamous epitheliomas, 4 basal cell epitheliomas and basal squamous or squamous cell epitheliomas and 7 single or multiple basal cell epitheliomas.

The occurrence of basal cell epithelioma in radiodermatitis does not appear to be incidental. In this series neoplasms developed in persons of a younger age group than is ordinarily reported. Furthermore, they occurred more than twice as frequently among women as among men, which is the reverse of the usual observation. These facts suggest that the basal cell epitheliomas present in these patients were, in most instances, associated with and related to the presence of the chronic radiodermatitis.

The trend in the literature has been to emphasize the association of squamous cell tumors with radiodermatitis. Montgomery [11] stated that it is questionable whether a basal cell epithelioma ever results from radiodermatitis and that its occasional association is probably coincidental. On the other hand, Warren [12] stated the belief that while epidermoid neoplasms are the more usual type, basal cell epitheliomas also may occur, which concurs also with the opinion of Andrews [13].

EXPERIMENTAL STUDIES

Since the exit dose in low voltage radiotherapy is of clinical significance, the previously published work of Andrews, Braestrup and Heisel [1] has been amplified. The present tables now include additional technics for use in the roentgen therapy of simple inflammatory dermatoses.

The methods used for the exit dose determinations have already been described in detail.[1] They will be summarized here only briefly. Measurements were taken with a condenser thimble type ionization chamber placed in close contact with the skin opposite the irradiated area. Regions studied were the dorsum and palm of the hand, the plantar surface of the foot just posterior to the toes and on the face, the surface of the distal ala nasi, when the cheek was treated. The sizes of the fields were comparable to fields used routinely for low voltage radiotherapy on these parts.

Two hundred and six readings were made for 91 persons. The previously published figures for 60 and 100 kilovolts unfiltered were

11. Montgomery, H., in MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in Treatment of Diseases of the Skin, Philadelphia, Lea & Febiger, 1946, p. 287.

12. Warren, S.: Effects of Radiation on Normal Tissues, Arch. Path. **35**:304 (Feb.) 1943.

13. Andrews, G. C.: Diseases of the Skin, ed. 3, Philadelphia, W. B. Saunders Company, 1946, p. 73.

confirmed; additional measurements were made for 80 kilovolts unfiltered and 100 kilovolts with 1 mm. of aluminum filter. Higher voltages were not included since they were considered neither practicable nor safe for use over relatively large areas in the treatment of benign dermatoses because of the high depth and exit doses.

Since the problem presented by the extremities is somewhat different from that of the face, it will be considered separately. Table 4 demonstrates the values determined on the hands and feet for the average exit dose expressed in percentage of the air dose for the ray qualities commonly used in dermatologic conditions. As expected, these

TABLE 4.—*Average Exit Dose, Expressed in Percentage of the Air Dose 15-30 Cm. (6-12 Inches) Target-Skin Distance* *

Irradiated Region	60 Kv., 0 Al., Half-Value Layer, 0.7 Al. Exit Dose, Percentage	80 Kv., 0 Al., Half-Value Layer, 0.8 Al. Exit Dose, Percentage	100 Kv., 0 Al., Half-Value Layer, 1.0 Al. Exit Dose, Percentage	100 Kv., 1 Al., Half-Value Layer, 2.0 Al. Exit Dose, Percentage
Hands	17.4	21.0	27.0	36.0
Feet	11.0	14.3	19.0	21.0

* The correction in percentage of exit dose required by using the percentages above over the range 15 to 30 cm. target-skin distance will be less than plus or minus 4 per cent.

TABLE 5.—*Air Dose to Give 100 Roentgens* * to Each Irradiated Cutaneous Surface When Using Opposing Fields*

Irradiated Region	60 Kv., 0 Al., Half-Value Layer, 0.7 Al. Air Dose	80 Kv., 0 Al., Half-Value Layer, 0.8 Al. Air Dose	100 Kv., 0 Al., Half-Value Layer, 1.0 Al. Air Dose	100 Kv., 1 Al., Half-Value Layer, 2.0 Al. Air Dose
Hands	80 r	76 r	70 r	65 r
Feet	86 r	81 r	73 r	70 r

* This value includes exit dose and back scatter.

figures show that the exit dose increases with the kilovoltage and filter. The highest values are obtained for the hands, the thinnest parts studied.

For the interpretation of these measurements from the practical point of view, table 5 presents data referring to the hands and feet and indicates the actual air dose required to deliver a skin dose of only 100 r to each irradiated cutaneous surface in the treatment of these sites.

It is apparent from table 5 that reductions of the air dose to the indicated values will offer greater protection when treating the extremities. Obviously if a skin dose of 75 r is desired the air dose should be reduced to three fourths of the aforementioned figures.

Although there is a slight variation in the values for the hands and feet, it is felt that this may be disregarded and that figures for the hands are applicable also to the feet. Actually, since the exit dose

decreases rapidly with an increasing thickness of the part, and, since treatment is often directed at the middle part of the foot, these figures are of relatively little importance unless repeated exposures are made directly over both surfaces of the toes. When therapy is used on the toes, the described values for the hands are practicable and should be applied.

The face presents a problem separate from the extremities, since the amount of radiation penetrating from one malar surface to the other is negligible because of the thickness and density of the head. Large quantities of radiation are received, however, by the middle part of the face owing to both the exit dose and overlapping.

TABLE 6.—*Dose in Roentgens on Each Ala Nasi When 100 Roentgens in Air is Given to Each Side of the Face**

60 Kv., 0 Al., Half-Value Layer, 0.7 Al.		80 Kv., 0 Al., Half-Value Layer, 0.8 Al.		100 Kv., 0 Al., Half-Value Layer, 1.0 Al.		100 Kv., 1 Al., Half-Value Layer, 2.0 Al.	
Air Dose	Ala Nasi Dose	Air Dose	Ala Nasi Dose	Air Dose	Ala Nasi Dose	Air Dose	Ala Nasi Dose
100 r	93 r	100 r	101 r	100 r	114 r	100 r	120 r

* With the central beam directed at the zygomaticofacial foramen.

TABLE 7.—*Air Dose Giving 100 Roentgens to Each Cheek When Each Side of the Face* is Treated*

	60 Kv., 0 Al., Half-Value Layer, 0.7 Al.	80 Kv., 0 Al., Half-Value Layer, 0.8 Al.
Air dose.....	94 r	90 r

* Central beam directed at the zygomaticofacial foramen.

The dose in roentgens given to each ala nasi when both cheeks are exposed to an air dose of 100 r is shown in table 6.

As table 6 indicates, the amount of radiation received by each ala nasi when the cheeks are treated is decidedly increased when a quality of 100 kilovolts is used. Therefore, in order to protect the middle part of the face, voltages in a range of 60 to 80 kilovolts are suggested. Further protection is insured by reducing the air dose as is shown in table 7.

With these factors, the amount of radiation delivered on the skin does not exceed 100 r either on each cheek surface or on the alae nasi. The variation in exit dosage for treatment of the face using target-skin distances of 15 and 30 cm. was studied and found to be negligible.

As pointed out by Andrews, Braestrup and Heisel,[1] it is obvious that a midface exposure in therapy is a further hazard when combined

with treatment to the sides of the face even when voltages as low as 60 kilovolts are used. This procedure should be abandoned entirely unless there is a decided reduction in the cheek dose or unless a midface exposure alone is used.

As has been already shown, the exit dose is influenced by physical factors, among which the following are of importance:

1. The quality of the radiation. The exit dose increases with the kilovoltage, which is one of the important reasons for the use of low voltage in the treatment of dermatoses.

2. The target-skin distance. The variation in the exit dose between 15 and 30 cm. distances in treatment of both the face and the extremities has been shown to be relatively unimportant, although the exit dose is somewhat higher at greater distances where the rays become more parallel. This applies, however, only to the range used ordinarily in dermatologic roentgen therapy. In contact therapy the exit dose is negligible because of the very short target-skin distance used.

3. The size of the field. The exit dose, like the depth dose, increases with the size of the field since there is an increased volume of irradiated tissue. Back scatter is, of course, also affected by the size of the field. However, our measurements have shown that the exit dose remains practically constant for field sizes discussed in this paper.

4. The thickness of the irradiated part. The exit dose diminishes rapidly with an increase in the thickness and density of the exposed tissue.

5. Underlying material. The exit dose is slightly higher when the treated part is resting on a scattering material, such as the mattress or pillow of the treatment table.

Using air doses of the described amounts and qualities, when repeated fractional exposures are given, there is decreased hazard of overdosage, which results from a summation of the air dose, back scatter and the exit dose. Greater protection is afforded, since determination is made of the dose of radiation actually delivered on the skin itself rather than the dose in air, which is misleading.

SUMMARY

One hundred and sixty cases of chronic radiodermatitis, 85 occurring after the treatment of benign dermatoses, have been reviewed with reference to the exit dose as a factor in the production of chronic roentgen injuries. Fifty-six patients were treated by irradiation, usually over prolonged periods of time, for conditions in which superficial therapy to opposing surfaces is still frequently used. Radiodermatitis was present frequently in this group on the middle part of the

face and the extremities, where the exit dose is high, and it may have been an additional factor in the production of radiation damage to the skin.

Tables are included enabling the dermatologist to take into account the exit and back scatter factors in roentgenotherapy of superficial dermatoses involving the face and extremities.

ABSTRACT OF DISCUSSION

DR. C. GUY LANE, Boston: It is of interest that the results of the work by Dr. Shafer and her co-workers confirm the fact that the exit dose is increased by an increase in kilovoltage or increase in filtration and increase with thickness of the part treated. They mention other factors as being of less importance. I believe that the tables which they have given will help us in treating lesions more confidently, especially on the face, hands and feet. They report 160 cases of radiodermatitis and 30 per cent, or 56 of the patients, have had repeated fractional treatments. One wonders whether the increased radiodermatitis on the face, that is, in about 25 cases, was due to the exit dose. The authors speak of overlapping and the custom of treating with the central area as additional factors, but their statement with regard to the observation of radiation changes in the nose, lips and chin would make one feel that the exit dose played a part here.

I was surprised to find there are only 7 cases of changes of the hand and 3 of the feet. Of course, one sees perhaps more cases of radiodermatitis of the hand, but those occur in technicians and radiologists and perhaps from intensive local treatment. There are comparatively few, apparently, in view of the number treated, in which radiodermatitis has occurred.

It is also of interest that in approximately half of the patients with radiodermatitis a carcinoma developed. I am aware of the possibility of the development of radiation carcinoma in all these cases. If these patients are seen five years or twenty years later, I think that one will find that a much higher percentage of radiation changes will have developed.

There are several lessons to be learned from this paper. The first would concern additional emphasis on the need of a strict accounting of total dosage in repeated fractional doses, not the number of treatments but the total amount of radiation given as repeated treatments are given. Total dosage of 400 or 500 r in blond persons may be sufficient, and a total of perhaps 1,200, in brunette persons is a dose which should not be exceeded. Secondly, the suggestion about giving up treatment in the midline when one is treating acne of the face should be seriously considered, or at least a lessening in the number of treatments to the midline when each side is given. The third suggestion concerns the care to be taken in the treatment of chronic diseases of the hands, regardless of the dosage, with regard to the agents which are used coincidentally with radiation. One should learn to omit treatment after four to six treatments if results are not beginning to be observed. Finally, it would seem that Dr. Shafer and her co-workers have emphasized well the six conditions in which one should use great care with reference to the exit dose, namely, acne, allergic diseases, conditions of the hands and feet, whatever dosage is given, sycosis, psoriasis and pruritis.

DR. I. L. SCHAMBERG, Philadelphia: I would like to ask about the effect of distance on irradiation of the face when roentgen rays are given parallel to a line drawn between the ears, as I believe is customary. I have found that the

distance to the nose was much greater than to the cheek and felt that I have given a smaller dose to the side of the nose than to the cheek on account of this distance factor.

From the slides presented, it appeared to me that decrease of dosage on the basis of distance would more than compensate for the increase on the basis of exit dose.

DR. STEPHEN EPSTEIN, Marshfield, Wis.: Dr. Shafer and her associates have presented a subject of great practical importance. In this day of technical improvements, the risk of unintentional overdosage has become much smaller than formerly. Exact physical measurement of the dose is available to everybody; the output of modern machines and x-ray tubes is astonishingly constant. Modern machines are equipped with exact and dependable timers that cut off the current automatically after the intended dose has been given. All these improvements and gadgets do not insure against mistakes, but they are a great help in this direction. Yet there remains the danger of unintentional damage to the skin by the hidden overdosage that may occur from improper overlapping and neglect of the exit dose, as has been shown so well by Dr. Shafer.

Some time ago I reported an analysis of 12 cases of radiodermatitis following what appeared to be normal or even small doses (*Arch. f. Dermat. u. Syph.* **168**: 548-571, 1933). In all instances overdosage due to overlapping had occurred. When the conditions under which the patients had been treated were reconstructed experimentally, it was found that the overdosage was considerable; in some instances, such as when the center of the face was treated, an increase up to 200 per cent over and above the intended dose was found. These cases had occurred in Europe where it was customary to have an additional midface exposure. In some places even two overlapping frontal fields, to forehead and chin, had been given. Therefore, I would like to stress the authors' recommendation that if a midface exposure is given at all, this must be counted as a full treatment. The evidence and tables given by the presenters may protect some of us and our patients from serious damage.

DR. ANTHONY C. CIPOLLARO, New York: Dr. Shafer, her co-workers and Dr. Andrews are to be congratulated for having instigated research in this important phase of dermatologic roentgen therapy, because their observations serve to emphasize the necessity of greater caution in treating ordinary inflammatory dermatoses with roentgen rays.

I would like to reiterate what has been emphasized in the paper: The cause for radiodermatitis is overdosage. Radiodermatitis is not caused by the exit dose alone; the exit dose is only one of the factors in a small percentage of the cases reported. Mostly it is due to poor judgment, frequent repetition of courses of treatment, improper calibration of the equipment, improper recording of each dose and failure on the part of the patient to reveal to the physician that roentgen rays had been previously applied. Occasionally, overanxiety on the part of the physician to cure a patient may cause him to apply more roentgen rays than is absolutely safe.

In the treatment of acne vulgaris of the face with roentgen rays only the sides of the face are exposed. A third exposure to the middle part of the face was abandoned years ago, because with such technic there may be too much overlapping and radiodermatitis may develop on the central portions of the face. The exit dose probably is never the cause of radiodermatitis of the face following the treatment of acne vulgaris and other diseases affecting the face.

In the treatment of eczema or other eruptions of the hands, exposure of the palmar and dorsal surfaces to roentgen rays of 100 kilovolts the exit dose increases the incident dose by about 25 per cent. If the total number of weekly treatments is limited to six or eight and each dose measured in air is 75 to 100 r, the additional amount of radiation derived from the exit dose and from secondary radiation would not be sufficient to produce radiodermatitis. Only with gross overdosage of roentgen rays to both sides of the hands does radiodermatitis ensue.

I do not believe that there is sufficient evidence to prove that most cases of radiodermatitis of the hands resulted from failure to take into consideration the exit dose. I concede that in an occasional case this can occur.

DR. JUNE C. SHAFER, New York: I thank the discussers for their valuable and stimulating discussion and also express my appreciation to Dr. George Andrews who made available his material and gave many valuable suggestions while the paper was being written. In reply to Dr. Schamberg, I would like to say that, as we have shown, radiation within the range of 60 to 80 kilovolts does not yield a dose on the skin of the nose of over 100 r when 100 r are given in air. When an amount over this dose is used, the exit dose on the ala nasi exceeds the dose in air. If computations are made when only one side of the face is treated, the figure is not important; but both sides of the face are treated, and, therefore, with treatment of one side of the face plus the exit dose the amount does become important. The variations with target-skin distances between a 15 to 30 cm. range were studied in the 60 to 80 kilovolt range and were important in regard, of course, to field size but not of great importance with reference to the variation in the exit dose. The exit dose, as Dr. Cipollaro has pointed out, is only one of the factors contributing to the production of radiodermatitis.

FAMILIAL PEMPHIGUS VULGARIS

Report of a Case

OTIS B. MILLER, M.D.
AND
LOUIS J. FRANK, M.D.
BROOKLYN

IN A SURVEY of 171 patients with pemphigus admitted to Bellevue Hospital from 1911 to 1941, Gellis and Glass [1] found no clear-cut evidence of familial involvement. Feldman [2] was the first to report in the American literature a case of familial pemphigus vulgaris, the disease occurring in 2 brothers who died ten years apart. In 1940, Greenbaum [3] reported that in a period of eighteen years he had observed the disease in a father and son, in sisters and, finally, in a husband and wife.

In view of the rareness of such observations, we feel that the following case of a woman whose 2 brothers had died of the disease should be reported.

REPORT OF CASE

R. M., a Russian Jewess aged 65, who had never been ill previously, in July 1946 had onset of a slight fever and sore mouth, with vesicles on the buccal mucosa and tongue. Penicillin brought the temperature to normal, but the vesicles persisted. For two months this condition, which was thought to be Vincent's angina, persisted and resisted all treatment. In September 1946 bullae suddenly developed over the entire body, together with a high fever. On being hospitalized, the patient showed extensive, generalized denudation and was given a high vitamin and high calory diet, intramuscular injections of liver extract, streptomycin, penicillin, carbarsone U. S. P., suramin sodium U. S. P. (naphuride sodium®) and, finally, promin® (N,N′-didextrose sulfonate, the sodium salt of p,p′-diaminodiphenyl sulfone). The response was poor; the lesions over the body cleared intermittently, but new ones always returned.

Fourteen months after the onset of her illness, on Aug. 12, 1947, the patient was admitted to Kings County Hospital. On physical examination, the striking finding was the great number of broken bullae and denudations present, on the

From the Department of Dermatology, Kings County Hospital.

1. Gellis, S., and Glass, F. A.: Pemphigus: A Survey of One Hundred and Seventy Patients Admitted to Bellevue Hospital from 1911 to 1941, Arch. Dermat. & Syph. **44**:321 (Sept.) 1941.

2. Feldman, S.: Pemphigus in Brothers, Arch. Dermat. & Syph. **33**:730 (April) 1936.

3. Greenbaum, S. S.: Cases of Familial and of Conjugal Pemphigus Vulgaris, Arch. Dermat. & Syph. **41**:1073 (June) 1940.

back, abdomen, hard palate, buccal mucosa, groin and extremities; scattered over the body were unruptured vesicles and bullae, together with crusting. The lips were sore and excoriated, the groin showed considerable exudation, and periorbital erythematous lesions were present bilaterally. The patient complained of a burning sensation of the skin, lethargy and anorexia, with loss of weight. A diagnosis of pemphigus vulgaris was made and confirmed at a staff conference.

Results of laboratory examinations are tabulated below:

Blood	Values/100 Cc.
Chemical constituents	
Total protein	3.8 Gm.
Albumin	2.2 Gm.
Globulin	1.6 Gm.
Urea	28. mg.
Sugar	76. mg.
Cholesterol	182. mg.
Sodium chloride	546. mg.
Sodium	310 mg.
Calcium	9.1 mg.
Cell count	
Red cells	3,010,000
White cells	11,000 (with normal differential)
Hemoglobin	6.5 Gm./100 cc.
Sedimentation rate	3.0 (in 45 min.)
Mazzini reaction	Negative
Urine	Negative

The family history is of special note: M. G., a brother, died of pemphigus at the age of 56, at City Hospital, New York, on March 13, 1916. H. G., another brother, a shoemaker, had been in the United States forty years at the time of his death, also at the age of 56, at Kings County Hospital, Feb. 18, 1932, with a diagnosis of pemphigus.

SUMMARY

This is the third report of familial pemphigus vulgaris in the American literature. The case here described is that of a woman whose 2 brothers died of the same disease, one sixteen and the other thirty-two years before she came to our attention.

Kings County Hospital.

Clinical Notes

SENSITIVITY TO TETRAETHYLAMMONIUM

Report of a Case

M. H. SAMITZ, M.D.
Chief, Clinic of Dermatology, Graduate Hospital of the University of Pennsylvania
AND
PETER N. HORVATH, M.D.*
PHILADELPHIA

Tetraethylammonium salts (bromide and chloride) are the latest drugs to find application in treatment of peripheral vascular diseases. They act on the ganglions of the autonomic nervous system by blocking the impulses peripheral to the ganglions.[1] The most important clinical application of these drugs is in conditions such as thrombophlebitis, peripheral arteriosclerosis obliterans, Raynaud's disease, thromboangiitis obliterans (Buerger's disease) and various other peripheral vascular disorders, in which the tone of blood vessels should be decreased.[2] We have found no report of cutaneous sensitivity to this drug, and we feel that the following case may be of significance.

REPORT OF CASE

B. M., a 46 year old white woman, had had trouble with varicose veins for seven years. In December 1946 a varicose ulcer developed on the pretibial area of the left leg, and the patient was given 200 mg. of tetraethylammonium chloride intravenously on March 8 and on March 22, 1947. After the second injection intense pruritus developed over her entire body, the itching being most pronounced on the face. At this time the patient was seen by one of us (M.H.S.); she presented a patch of contact dermatitis due to local medication, over the pretibial area of the left leg, and the rest of her skin was covered with excoriations.

She was treated conservatively, and the lesions cleared up almost entirely, except for minimal activity around the varicose ulcer, by August 1947. During October 1947 she had another episode of thrombophlebitis.

On Oct. 29, 1947, she received another injection of tetraethylammonium chloride (200 mg. intravenously), and within four to six hours severe, intractable, generalized pruritus developed; the condition became unbearable in two days, and the patient had to be hospitalized. On examination she had minimal oozing and crusting over the pretibial area of the left leg, with no cutaneous lesions except excoriation marks distributed over the entire body.

She was treated with procaine hydrochloride, administered intravenously; tripelennamine hydrochloride (pyribenzamine hydrochloride®), orally, and saline soaks. She made an uneventful recovery in two weeks.

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*Fellow in Dermatology, University of Pennsylvania.

1. Acheson, G. H., and Moe, G. K.: J. Pharmacol. & Exper. Therap. **87**:220, 1946.

2. Berry, R. L., and others: Surgery **20**:525, 1946. Lyons, R. H., and others: Univ. Hosp. Bull., Ann Arbor **12**:33, 1946. Lyons, R. H., and others: Am. J. M. Sc. **213**:315, 1947. Coller, F. A., and others: Ann. Surg. **125**:729, 1947.

COMMENT

A review of the literature[2] disclosed toxic effects of tetraethylammonium attributable only to the physiologic actions of the drug. These consist in an increase in the pulse rate, a drop in both the systolic and the diastolic blood pressure, dryness of the mouth, absence of sweating and a metallic taste in the mouth. While the mechanism of the pruritus induced in our patient was somewhat obsecure, there seemed to be a definite relation between the administration of the tetraethylammonium chloride and the onset of the pruritus. Possibly the generalized vasodilatation played a role in producing pruritus, or the pruritus may have been an expression of sensitivity to the drug. Because of the severity of the pruritus, tests for sensitivity were thought to be too risky. In any event, the case history leads us to the conclusion that the administration of tetraethylammonium is not entirely free of allergic manifestations.

DERMATITIS MEDICAMENTOSA (FIXED TYPE) FROM USE OF 666 FOR COLDS®

EARL B. RITCHIE, M.D.
AND
WILLIAM F. SPILLER, M.D.
GALVESTON, TEXAS

Recently we had referred to us a white man, aged 25, who presented an eruption consisting of large, dusky, erythematous and scaly macules, scattered over the shoulders, arms and thighs. The eruption had been present for five months. A tentative diagnosis of dermatitis medicamentosa of the fixed type was made.

Histologic examination showed subacute nonspecific inflammation, with melanin in the chromatophores. Stains of tissue smears and sections were negative for acid-fast organisms. The serologic reactions for syphilis were negative, and the blood count revealed no abnormaltities.

The patient when questioned revealed that he was a periodic user of 666 for Colds.® [1] He was advised to discontinue use of this preparation and was given 1 Gm. of sodium thiosulfate intravenously. Three days later the eruption had subsided, with only residual hyperpigmentation. We then asked the patient to take his usual does of 666® and return the next day. This action resulted in a pronounced flare-up in the same areas in which the eruption had previously appeared.

The preparation 666 for Colds® contains 10 grains (650 mg.) of antipyrine U. S. P. XII to the ounce (28.35 Gm.) and ammonium chloride, magnesium sulfate and citric acid (amounts of the last three ingredients not given on the label). When the eruption had subsided from the test dose of 666,® the patient was given 2½ grains (162 mg.) of antipyrine and when seen twenty-four hours later showed again a pronounced flare-up in the original sites of eruption.

The patient then remembered that he occasionally took tablets of 666.® These contain 2½ grains of acetophenetidin, along with phenolphthalein and ammonium

1. Monticello Drug Co., Jacksonville, Fla.

chloride (amounts not given), to each tablet. A test dose with 1 grain (65 mg.) of phenolphthalein failed to cause a reaction in the fixed sites.

He was then given 50 mg. of tripelennamine hydrochloride (pyribenzamine hydrochloride®) and thirty minutes later 65 mg. of antipyrine. The following day he again showed a very decided recrudescence of the original eruption. We had hoped to test him with a larger preliminary dose of tripelennamine hydrochloride and to the other ingredients of 666,® both in tablet and in liquid form, but he was reluctant to continue, fearing that further investigation would be harmful.

SUMMARY AND CONCLUSION

A "fixed eruption" due to antipyrine contained in 666 for Colds® is described. Administration of 50 mg. of tripelennamine hydrochloride thirty minutes before 65 mg. of antipyrine was taken failed to prevent a recrudescence of the eruption.

906 Twenty-Second Street.

ERYTHEMA ANNULARE CENTRIFUGUM TREATED WITH SULFONAMIDE COMPOUNDS

ERVIN EPSTEIN, M.D.
OAKLAND, CALIF.

Peterkin[1] in 1945 published a report concerning a patient with erythema annulare centrifugum treated by the oral administration of sulfathiazole. The author characterized the improvement in his patient as "dramatic." A 28 year old man had noted this condition for one month prior to the institution of sulfathiazole therapy. Within three days only pigmentation persisted. The patient was discharged from the hospital after one week, apparently cured. Unfortunately, Peterkin was unable to follow this patient, and so the ultimate result is not known.

Obviously, the results obtained in 1 case do not establish the efficacy of any therapeutic agent. This fact is especially to be kept in mind in the case of a capricious disease such as erythema annulare centrifugum. Therefore, the case here reported is presented as another instance in which this dermatosis responded to treatment with sulfonamide compounds.

REPORT OF A CASE

C. M., a 13 year old white school girl, was first seen on Jan. 12, 1946, because of a mildly pruritic eruption of two and one-half months' duration. The patient had taken a proprietary laxative preparation containing phenolphthalein (ex-lax®) every two weeks since the age of 5 years. There were no symptoms suggestive of rheumatic fever.

On examination she presented a bizarre eruption involving her neck, trunk and extremities. Lesions were present in all stages of evolution. The individual lesions apparently started as erythematous papules, which enlarged peripherally, forming a flesh-colored or erythematous, firm border with a lightly pigmented center. The border was slightly but definitely elevated. The lesions varied from

1. Peterkin, G. A. G.: A Case of Erythema Annulare Centrifugum, Brit. J. Dermat. **57**:65 (March-April) 1945.

papules the size of a pinhead to those that covered an area the size of a palm. Many were discrete, but others coalesced to form gyrate patterns. Observation established the fact that the lesions were evanescent, the individual lesions clearing in two to six weeks, to be replaced by new ones. There was no permanent residual pigmentation.

Histologic examination of a piece of skin removed from the active border of a lesion showed the pathologic alterations to be confined to the derma. There was considerable edema, with vascular dilatation. A nodular inflammatory infiltrate was scattered through the central and upper portions of the corium. This infiltrate was basically lymphocytic but contained many eosinophils.

An intradermal tuberculin test gave a negative reaction. The reactions to the Kolmer, Kahn and Kline tests of the blood were also negative. Urinalyses repeatedly showed normal constituents.

The patient was presented before the San Francisco Dermatological Society on March 2, 1946, and before the combined meeting of the San Francisco and the Los Angeles Dermatological Societies on Jan. 18, 1947. At both meetings, the discussants agreed on the diagnosis of erythema annulare centrifugum.

Therapy included superficial roentgen irradiation, untraviolet irradiation and intravenous injections of calcium and of nicotinamide. All use of laxatives was discontinued for more than twenty months. Only two measures, however, seemed to be efficacious. Diphenhydramine hydrochloride (benadryl hydrochloride®) apparently caused improvement in the eruption, but this was not definite.

On Aug. 14, 1946, treatment with sulfadiazine, in doses of 0.5 Gm. administered four times a day, was instituted. On August 24, the eruption had nearly cleared. However, this treatment was discontinued because of possible toxicity, and the dermatosis occurred in severity equaling that of the presulfadiazine state. The treatment was resumed on Jan. 21, 1947, and the condition quickly subsided. In May the patient discontinued the treatment, and the eruption recurred. Administration of sulfapyridine (N. F.) in doses of 0.5 Gm. twice a day was instituted, and the lesions promptly cleared. Since then, the dose of sulfapyridine has been decreased until, at the time of this report in October 1947, the patient was taking 1 tablet (0.5 Gm.) of sulfapyridine N. F. every two days. Her skin has remained clear. The patient found that if she discontinued the sulfapyridine the eruption recurred in about two weeks. Attempts are still being made to determine the irreducible minimum that will prevent recurrences.

COMMENT

Many agents have been suggested for the treatment of erythema annulare centrifugum. Articles have been published extolling the benefits obtained by the use of potassium arsenite solution U. S. P. and by injections of bismuth. However, in this case at least, sulfonamide drugs seemed to exert a specific effect on the eruption. The condition cleared promptly on the administration of sulfonamide drugs and recurred on their withdrawal, and a small maintenance dose seemed to minimize the possibility of recurrences. This situation suggests the results obtained by these drugs in treatment of dermatitis hepetiformis. Rather than proving a relationship between these two conditions, the evidence presented merely suggests that sulfonamide compounds may be as specific for erythema annulare centrifugum as they are for dermatitis hepetiformis.

SUMMARY

A case of erythema annulare centrifugum is presented in which sulfadiazine and sulfapyridine temporarily eradicated the eruption and prevented recurrences as long as small doses of these agents were continued.

NOTE.—On Dec. 23, 1948, decided albuminuria was noted. Treatment with the sulfonamide drugs was discontinued, and the eruption recurred in severity equal to the worst it had been in the past. The albuminuria quickly subsided, but no further sulfonamide therapy has been given.

447 Twenty-Ninth Street.

ANAL COMEDOS AND PRURITUS ANI

H. V. ALLINGTON, M.D.
OAKLAND, CALIF.

I have found that perianal comedos have been the cause of severe pruritus ani in at least 1 patient.

An experienced dermatologist came to me for treatment of pruritus ani. Inspection revealed about six large comedos around the anal orifice. One was as large as a small pea. All had hard, horny spines projecting above the surface of the skin. Removal of the comedos was followed within a few minutes by disappearance of the pruritus.

Several years later the pruritus recurred; more comedos were found and were expressed, and the pruritus immediately disappeared.

The fact that the projecting horny portions of the comedos came in contact with the fecal mass may have accounted for the intense pruritus which followed each defecation.

Microscopic examination of the comedos revealed the presence of many Demodex folliculorum organisms.

3115 Webster Street (9).

Obituaries

HOWARD TROY PHILLIPS, M.D.

1891-1949

Dr. Howard Troy Phillips, Wheeling, W. Va., was born in St. George, W. Va., on Aug. 19, 1891. He was educated at Shepardstown College and West Virginia University. He graduated in medicine at Western Reserve University in 1920. He took postgraduate work in dermatology in Cleveland and New York. He practiced dermatology in Wheeling from 1923. During World War I he served in the United States Navy. He was a member of his county and state medical associations and of the American Medical Association, a certified specialist of the American Board of Dermatology and Syphilology and a member of the Pittsburgh Dermatological Society, the Central States Dermatological Association and the American Academy of Dermatology and Syphilology. He was recently appointed to the faculty of the University of Pittsburgh School of Medicine.

Dr. Phillips was killed in an automobile accident on March 7, 1949. He is survived by his wife and three sons. Dr. Phillips gave freely of his time in training young men. He was universally held in high esteem by his patients and his contemporaries in dermatology. In the best possible meaning of the term he was a good physician.

W. H. Guy, M.D.

News and Comment

GENERAL NEWS

British Association to Meet in July.—Dr. J. E. M. Wigley, honorary secretary of the British Association of Dermatology and Syphilology, has announced that dermatologists from the United States will be welcome at the Annual Meeting of the British Association of Dermatology and Syphilology in London on July 7, 8 and 9, 1949. The principal subject for discussion will be "The Action and Uses of the Antihistamine Drugs as Applied to Dermatology," and the discussion will be opened by Sir Henry Dale.

Book Reviews

The Biology of Melanomas. By Myron Gordon and others. Vol. 4. Price, $5. Pp. 466. New York: New York Academy of Sciences, 1948.

This book is the result of the Conference on the Biology of Normal and Atypical Pigment Cell Growth, held by the Section of Biology of the New York Academy of Sciences, November 1946. It represents a correlation of the knowledge of types of pigment cells, pigment formation and melanomas, both benign and malignant, in human beings and various animals. Cytology, tissue culture, physiology, chemistry, genesis, influence of light and endocrines on pigment formation and tissue metabolism are considered in different chapters by leading authorities in these fields. The book is an excellent correlation of all known facts concerning melanogenesis. Dermatologists will be especially interested in the chapters on pigment cells by Masson, on pigmented nevi by Pack, melanomas by Macdonald, melanin pigmentation by Becker, genetic aspects of pigment cell growth by Macklin and light and melanin pigment of the skin by Blum. The book is well arranged and contains many excellent illustrations. It can be recommended to all physicians who are interested in the formation of melanin pigment in the skin and in benign and malignant conditions related thereto.